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  This file contains CAS Registry Numbers for easy and accurate
  substance identification.

=> d que
L1          278 SEA FILE=CAPLUS (S(W)OMEPRAZOLE OR ESOMEPRAZOLE)
L3            6 SEA FILE=CAPLUS L1 AND AMORPH?


=> d l3 1-6 fbib abs hit

L3   ANSWER 1 OF 6  CAPLUS  COPYRIGHT 2005 ACS on STN
AN   2004:944187  CAPLUS
TI   Method for preparing solid, optically pure and neutral S-(-)- and
     R-(+)-omeprazole
IN   Deng, Jingen; Chi, Yongxiang; Liao, Jian; Cui, Xin; Fu, Fangmin; Jiang,
     Yaozhong
PA   Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, Peop.
     Rep. China
SO   Faming Zhuanli Shenqing Gongkai Shuomingshu, 14 pp.
     CODEN: CNXXEV
DT   Patent
LA   Chinese
FAN.CNT 1
     PATENT NO.          KIND   DATE        APPLICATION NO.          DATE
     ---------------     ----   --------    --------------------     --------
PI   CN 1467207           A     20040114    CN 2003-135164           20030610
                                             CN 2003-135164           20030610
AB   The method comprises dissolving oily or pulpous R-(+)- or S-(-)-
     omeprazole in 4-10% NaOH solution (at a molar ratio of 1:0.5- 3.0)
     for 1-2 h to pH 10-11, concentrating, adding water-soluble organic solvent,
adding
     inorg. acidic salt or Me formate at -0° to pH 7.5-10.0, stirring
     for 0.5-4 h, standing at (-20)- 0° for 10-24 h, vacuum drying the
     precipitate at room temperature for 10-20 h to obtain amorphous and optically
     pure omeprazole, and recrystg. in water-organic solvent.  The organic solvent
is
     C<6 alc., ketone, or ether, preferably butanone.  The inorg. acidic salt
     is KHSO4, NaHCO3, KH2PO4, and/or NaH2PO4.  The optically pure omeprazole
     crystal may be used for preventing and treating gastric acid
     secretion-related diseases, treating gastrointestinal bleeding and ulcer,
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and also treating psoriasis.

AB The method comprises dissolving oily or pulpous R-(+)- or **S**-(-)-**omeprazole** in 4-10% NaOH solution (at a molar ratio of 1:0.5- 3.0) for 1-2 h to pH 10-11, concentrating, adding water-soluble organic solvent, adding inorg. acidic salt or Me formate at -0° to pH 7.5-10.0, stirring for 0.5-4 h, standing at (-20)- 0° for 10-24 h, vacuum drying the precipitate at room temperature for 10-20 h to obtain **amorphous** and optically pure omeprazole, and recrystg. in water-organic solvent. The organic solvent is C<6 alc., ketone, or ether, preferably butanone. The inorg. acidic salt is KHSO4, NaHCO3, KH2PO4, and/or NaH2PO4. The optically pure omeprazole crystal may be used for preventing and treating gastric acid secretion-related diseases, treating gastrointestinal bleeding and ulcer, and also treating psoriasis.

IT INDEXING IN PROGRESS

IT 119141-88-7P, **S**-(-)-**Omeprazole**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparing solid, optically pure and neutral S-(-)- and R-(+)-omeprazole)

L3 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2004:368926 CAPLUS
DN 140:363011
TI **Amorphous** form of **esomeprazole** salts
IN Khanna, Mahavir Singh; Vijayaraghavan, Bakthavathsalan; Prasad, Mohan; Kumar, Yatendra
PA Ranbaxy Laboratories Limited, India
SO PCT Int. Appl., 17 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2004037253	A1	20040506	WO 2003-IB4662	20031022
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
			IN 2002-DE1057	A 20021022
US 2004235903	A1	20041125	US 2003-690897	20031022
			IN 2002-DE1057	A 20021022

AB The invention relates to an **amorphous** form of the salts of the (-) enantiomer of omeprazole, i.e., **esomeprazole**. Alkali metal or alkaline earth metal salts of **esomeprazole** are more stable during storage than the corresponding neutral form. The invention also relates to processes for preparing **amorphous** salts and pharmaceutical compns. that include the **amorphous esomeprazole** salts.

RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI **Amorphous** form of **esomeprazole** salts

AB The invention relates to an **amorphous** form of the salts of the (-) enantiomer of omeprazole, i.e., **esomeprazole**. Alkali metal or alkaline earth metal salts of **esomeprazole** are more stable during storage than the corresponding neutral form. The invention also relates to processes for preparing **amorphous** salts and pharmaceutical

compns. that include the **amorphous esomeprazole** salts.

ST **amorphous esomeprazole** metal salt

IT Alcohols, miscellaneous
RL: MSC (Miscellaneous)
(lower; solvents for preparation of **amorphous** form of **esomeprazole** salts)

IT Esters, miscellaneous
Ketones, miscellaneous
RL: MSC (Miscellaneous)
(solvents for preparation of **amorphous** form of **esomeprazole** salts)

IT 161796-78-7, **Esomeprazole** sodium 161796-84-5 161796-85-6
161973-10-0, **Esomeprazole** magnesium
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**amorphous** form of **esomeprazole** salts)

IT 64-17-5, Ethanol, miscellaneous 67-56-1, Methanol, miscellaneous
67-63-0, Isopropanol, miscellaneous 67-64-1, Acetone, miscellaneous
67-66-3, Chloroform, miscellaneous 71-23-8, Propanol, miscellaneous
71-36-3, Butanol, miscellaneous 75-05-8, Acetonitrile, miscellaneous
75-09-2, Dichloromethane, miscellaneous 75-65-0, tert-Butanol, miscellaneous 78-83-1, Isobutanol, miscellaneous 78-93-3, 2-Butanone, miscellaneous 108-10-1, 4-Methylpentan-2-one 123-86-4, Butyl acetate
141-78-6, Ethyl acetate, miscellaneous
RL: MSC (Miscellaneous)
(solvents for preparation of **amorphous** form of **esomeprazole** salts)

L3 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2004:354792 CAPLUS
DN 140:327137
TI Stable solid preparations containing **amorphous** benzimidazoles and salts
IN Nonomura, Muneo; Ito, Hiroki; Hashimoto, Hideo; Urai, Tadashi
PA Takeda Chemical Industries, Ltd., Japan
SO PCT Int. Appl., 51 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004035052	A1	20040429	WO 2003-JP13152	20031015
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
				JP 2002-301893 A	20021016
	JP 2004155773	A2	20040603	JP 2003-354904	20031015
				JP 2002-301893 A	20021016

OS MARPAT 140:327137

AB It is intended to provide a process for producing unstable **amorphous** benzimidazole compds. having a proton pump inhibitor function, and stable solid prepns. for medicinal use containing these compds. which are produced by blending such an **amorphous** benzimidazole compound with a nontoxic base such as a basic inorg. salt, forming an

intermediate coating layer on the layer containing the active ingredient and further forming an enteric coating layer or a release-controlling coating layer. For example, granules were formulated containing **amorphous** (R)-lansoprazole, MgCO3, and excipients, treated with an enteric-soluble coating composition containing methacrylate copolymer, then filled into capsules.

RE.CNT 164 THERE ARE 164 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Stable solid preparations containing **amorphous** benzimidazoles and salts

AB It is intended to provide a process for producing unstable **amorphous** benzimidazole compds. having a proton pump inhibitor function, and stable solid prepns. for medicinal use containing these compds. which are produced by blending such an **amorphous** benzimidazole compound with a nontoxic base such as a basic inorg. salt, forming an intermediate coating layer on the layer containing the active ingredient and further forming an enteric coating layer or a release-controlling coating layer. For example, granules were formulated containing **amorphous** (R)-lansoprazole, MgCO3, and excipients, treated with an enteric-soluble coating composition containing methacrylate copolymer, then filled into capsules.

ST **amorphous** benzimidazole proton pump inhibitor salt granule stability; lansoprazole magnesium carbonate granule enteric coating capsule

IT Drug delivery systems
(capsules; stable solid prepns. containing **amorphous** benzimidazole proton pump inhibitors and salts)

IT Transport proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(proton pump, inhibitors; stable solid prepns. containing **amorphous** benzimidazole proton pump inhibitors and salts)

IT Drug delivery systems
(solids, enteric-coated; stable solid prepns. containing **amorphous** benzimidazole proton pump inhibitors and salts)

IT 313640-86-7
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stable solid prepns. containing **amorphous** benzimidazole proton pump inhibitors and salts)

IT 144-55-8, Sodium hydrogen carbonate, biological studies 471-34-1, Calcium carbonate, biological studies 497-19-8, Sodium carbonate, biological studies 546-93-0, Magnesium carbonate 1309-42-8, Magnesium hydroxide 1309-48-4, Magnesia, biological studies 1343-88-0, Magnesium silicate 7647-14-5, Sodium chloride, biological studies 12304-65-3, Hydrotalcite 21645-51-2, Aluminum hydroxide, biological studies 119141-88-7, **S-Omeprazole** 119141-89-8 138530-94-6 138530-95-7, S-Lansoprazole 142678-35-1, S-Pantoprazole 142706-18-1 177795-59-4, S-Rabeprazole 177795-60-7
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stable solid prepns. containing **amorphous** benzimidazole proton pump inhibitors and salts)

L3 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2004:203830 CAPLUS
DN 140:245456
TI **Amorphous** hydrates of **esomeprazole** magnesium and a process for their preparation
IN Reddy, Manne Satyanarayana; Kumar, Muppa Kishore; Purandhar, Koilkonda; Sreenath, Keshaboina
PA Reddy's Laboratories Limited, India; Reddy's Laboratories, Inc.
SO PCT Int. Appl., 31 pp.
CODEN: PIXXD2

DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2004020436	A1	20040311	WO 2003-US27177	20030828
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
			IN 2002-MA638	A 20020830
US 2004167173	A1	20040826	US 2003-651306	20030828
			IN 2002-MA638	A 20020830

OS MARPAT 140:245456

AB A trihydrate of **esomeprazole** magnesium in the form of an **amorphous** solid is prepared and described for use as a gastric acid inhibitor.

RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI **Amorphous** hydrates of **esomeprazole** magnesium and a process for their preparation

AB A trihydrate of **esomeprazole** magnesium in the form of an **amorphous** solid is prepared and described for use as a gastric acid inhibitor.

ST **esomeprazole** magnesium hydrate manuf antacid

IT Alcohols, uses
RL: NUU (Other use, unclassified); USES (Uses)
(aliphatic, solvents; process for preparation of **amorphous** hydrates of **esomeprazole** magnesium for use in reducing gastric acid secretion)

IT Alkanes, uses
RL: NUU (Other use, unclassified); USES (Uses)
(halo, solvents; process for preparation of **amorphous** hydrates of **esomeprazole** magnesium for use in reducing gastric acid secretion)

IT Human
Polymorphism (crystal)
(process for preparation of **amorphous** hydrates of **esomeprazole** magnesium for use in reducing gastric acid secretion)

IT Gastric acid
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(secretion, inhibitors; process for preparation of **amorphous** hydrates of **esomeprazole** magnesium for use in reducing gastric acid secretion)

IT Ulcer
(treatment; process for preparation of **amorphous** hydrates of **esomeprazole** magnesium for use in reducing gastric acid secretion)

IT 161973-10-0, **Esomeprazole** magnesium
RL: RCT (Reactant); RACT (Reactant or reagent)
(hydration in process for preparation of **amorphous** hydrates of **esomeprazole** magnesium)

IT 217087-09-7P 668985-31-7P
RL: IMF (Industrial manufacture); PRP (Properties); SPN (Synthetic

preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(process for preparation of **amorphous** hydrates of **esomeprazole** magnesium for use in reducing gastric acid secretion)

IT 7439-95-4, Magnesium, reactions 161796-78-7, **Esomeprazole** sodium
RL: RCT (Reactant); RACT (Reactant or reagent)
(process for preparation of **amorphous** hydrates of **esomeprazole** magnesium for use in reducing gastric acid secretion)

IT 119141-88-7P, **Esomeprazole**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(process for preparation of **amorphous** hydrates of **esomeprazole** magnesium for use in reducing gastric acid secretion)

IT 64-17-5, Ethanol, uses 67-56-1, Methanol, uses 67-66-3, Trichloromethane, uses 71-23-8, Propanol, uses 71-36-3, Butanol, uses 75-09-2, Dichloromethane, uses 141-78-6, Ethyl acetate, uses 1300-21-6, Dichloroethane
RL: NUU (Other use, unclassified); USES (Uses)
(solvent; process for preparation of **amorphous** hydrates of **esomeprazole** magnesium for use in reducing gastric acid secretion)

IT 7732-18-5, Water, reactions
RL: NUU (Other use, unclassified); RCT (Reactant); RACT (Reactant or reagent); USES (Uses)
(solvent; process for preparation of **amorphous** hydrates of **esomeprazole** magnesium for use in reducing gastric acid secretion)

L3 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2004:20682 CAPLUS
DN 140:77151
TI process for preparation of optically pure or optically enriched sulfoxides, including **amorphous esomeprazole** and salts thereof, via resolution using transition metal complexes.
IN Reddy, Manne Satyanarayana; Kumar, Muppa Kishore; Reddy, Kikkuru Srirami; Purandhar, Koilkonda; Sreenath, Keshaboina
PA Reddy's Laboratories Limited, India; Reddy's Laboratories, Inc.
SO PCT Int. Appl., 35 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2004002982	A2	20040108	WO 2003-US20250	20030627
WO 2004002982	A3	20040610		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

IN 2002-MA489	A	20020627	
IN 2002-MA493	A	20020628	

US 2004077869	A1	20040422	US 2003-608781		20030627
			IN 2002-MA489	A	20020627
			IN 2002-MA493	A	20020628
EP 1515963	A2	20050323	EP 2003-762106		20030627
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK					
			IN 2002-MA489	A	20020627
			IN 2002-MA493	A	20020628
			WO 2003-US20250	W	20030627

OS MARPAT 140:77151

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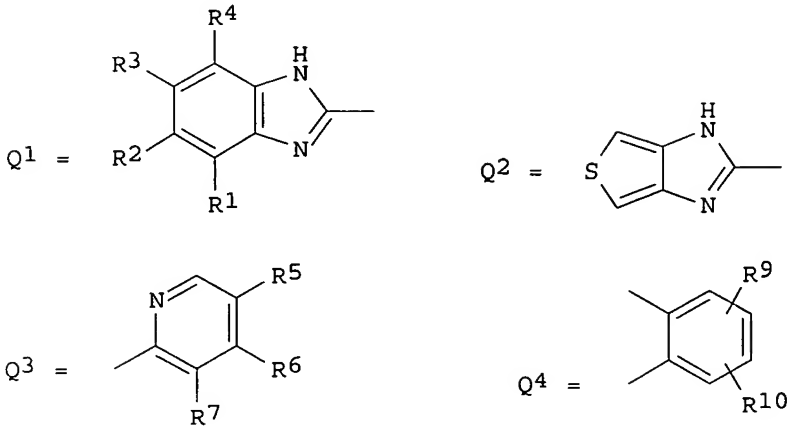

AB Title process comprises (a) providing, in an organic solvent, a mixture of optical isomers of R'SOXR'' [R' = Q1, Q2; R'' = Q3; X = CHR8, Q4; R1-R4 = H, alkyl, alkoxy, halo, haloalkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl; R5-R7 = H, alkyl, haloalkyl, alkylthio, haloalkylthio, alkoxy, haloalkoxy, alkoxyalkoxy, dialkylamino, piperdino, morpholino, halo, phenylalkyl, phenylalkoxy; R8 = H, alkyl; R9, R10 = H, halo, alkyl, alkoxy] (b) reacting the mixture with a coordinating agent containing a transition metal and a chelating agent to form a mixture of transition metal complexes at the sulfoxide group; (c) reacting the mixture of transition metal complexes with an organic acid (salt), which is capable of forming an addition product with the transition metal complex, wherein ≥1 of the chelating agent or the organic acid contains a chiral center and is substantially enantiomerically pure; thereby each of the transition metal complexes of the optical isomers forms an adduct with the organic acid or a salt thereof, the different adducts having ≥1 phys. property in which they differ from one another; (d) separating 1 of the adducts from the other based on ≥1 different phys. property; treating the separated adduct with an acid or base to decompose the complex thereby obtaining a product that is one of the optical isomers of the sulfoxide compound in a substantially optically pure or optically enriched form. Thus, omeprazole sodium (preparation given) in acetone was treated sequentially at 35-40° with di-Et D-tartrate, titanium tetraisopropoxide, Et3N, and L-mandelic acid followed by stirring to precipitate the L-mandelic acid titanium complex salt of **esomeprazole** in 99.78% chiral purity. This was suspended in CH2Cl2/aqueous NaHCO3 followed by stirring, separation of the CH2Cl2 layer, and evaporation to give **esomeprazole** in 99.85% chiral purity.

TI process for preparation of optically pure or optically enriched sulfoxides, including **amorphous esomeprazole** and salts thereof, via resolution using transition metal complexes.

AB Title process comprises (a) providing, in an organic solvent, a mixture of

optical isomers of R'SOXR'' [R' = Q1, Q2; R'' = Q3; X = CHR8, Q4; R1-R4 = H, alkyl, alkoxy, halo, haloalkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl; R5-R7 = H, alkyl, haloalkyl, alkylthio, haloalkylthio, alkoxy, haloalkoxy, alkoxyalkoxy, dialkylamino, piperdino, morpholino, halo, phenylalkyl, phenylalkoxy; R8 = H, alkyl; R9, R10 = H, halo, alkyl, alkoxy] (b) reacting the mixture with a coordinating agent containing a transition metal and a chelating agent to form a mixture of transition metal complexes at the sulfoxide group; (c) reacting the mixture of transition metal complexes with an organic acid (salt), which is capable of forming an addition product with the transition metal complex, wherein ≥1 of the chelating agent or the organic acid contains a chiral center and is substantially enantiomerically pure; thereby each of the transition metal complexes of the optical isomers forms an adduct with the organic acid or a salt thereof, the different adducts having ≥1 phys. property in which they differ from one another; (d) separating 1 of the adducts from the other based on ≥1 different phys. property; treating the separated adduct with an acid or base to decompose the complex thereby obtaining a product that is one of the optical isomers of the sulfoxide compound in a substantially optically pure or optically enriched form. Thus, omeprazole sodium (preparation given) in acetone was treated sequentially at 35-40° with di-Et D-tartrate, titanium tetraisopropoxide, Et3N, and L-mandelic acid followed by stirring to precipitate the L-mandelic acid titanium complex salt of **esomeprazole** in 99.78% chiral purity. This was suspended in CH2Cl2/aqueous NaHCO3 followed by stirring, separation of the CH2Cl2 layer, and evaporation to give **esomeprazole** in 99.85% chiral purity.

ST omeprazole resoln transition metal complex; **esomeprazole** **amorphous** prepn; sulfoxide resoln chelating agent transition metal org acid; gastric acid secretion inhibitor **amorphous** **esomeprazole** prepn

IT Ulcer
(gastric, treatment; process for preparation of optically pure or optically enriched sulfoxides, including **amorphous esomeprazole** and salts thereof, via resolution using transition metal complexes)

IT Chelating agents
Drug delivery systems
Resolution (separation)
(process for preparation of optically pure or optically enriched sulfoxides, including **amorphous esomeprazole** and salts thereof, via resolution using transition metal complexes)

IT Sulfoxides
RL: IMF (Industrial manufacture); PUR (Purification or recovery); SPN (Synthetic preparation); PREP (Preparation)
(process for preparation of optically pure or optically enriched sulfoxides, including **amorphous esomeprazole** and salts thereof, via resolution using transition metal complexes)

IT Transition metal complexes
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(process for preparation of optically pure or optically enriched sulfoxides, including **amorphous esomeprazole** and salts thereof, via resolution using transition metal complexes)

IT Gastric acid
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(secretion, inhibitors; process for preparation of optically pure or optically enriched sulfoxides, including **amorphous** **esomeprazole** and salts thereof, via resolution using transition metal complexes)

IT Stomach, disease
(ulcer, treatment; process for preparation of optically pure or optically enriched sulfoxides, including **amorphous esomeprazole** and salts thereof, via resolution using transition metal complexes)

IT 7439-95-4DP, Magnesium, **Esomeprazole** complex 119141-88-7P, **Esomeprazole** 119141-89-8P 161796-78-7P 161796-84-5P
RL: IMF (Industrial manufacture); PUR (Purification or recovery); SPN (Synthetic preparation); PREP (Preparation)
(process for preparation of optically pure or optically enriched sulfoxides, including **amorphous esomeprazole** and salts thereof, via resolution using transition metal complexes)

IT 611-71-2DP, D-Mandelic acid, Omeprazole-Titanium complex 7440-32-6DP, Titanium, **Esomeprazole** and Omeprazole complexes 17199-29-0DP, L-Mandelic acid, **Esomeprazole**-Titanium complex 119141-88-7DP, **Esomeprazole**, Titanium and Magnesium complexes 119141-89-8DP, (+)-Omeprazole, Titanium complex
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(process for preparation of optically pure or optically enriched sulfoxides, including **amorphous esomeprazole** and salts thereof, via resolution using transition metal complexes)

IT 56-23-5, Carbon tetrachloride, uses 67-56-1, Methanol, uses 67-64-1, Acetone, uses 67-66-3, Chloroform, uses 75-05-8, Acetonitrile, uses 75-09-2, Dichloromethane, uses 78-93-3, Methyl ethyl ketone, uses 96-22-0, Diethyl ketone 108-10-1, Methyl isobutyl ketone 141-78-6, Ethyl acetate, uses 1300-21-6, Dichloroethane
RL: NUU (Other use, unclassified); USES (Uses)
(process for preparation of optically pure or optically enriched sulfoxides, including **amorphous esomeprazole** and salts thereof, via resolution using transition metal complexes)

IT 73590-58-6, Omeprazole
RL: RCT (Reactant); RACT (Reactant or reagent)
(process for preparation of optically pure or optically enriched sulfoxides, including **amorphous esomeprazole** and salts thereof, via resolution using transition metal complexes)

IT 95510-70-6P, Omeprazole sodium
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(process for preparation of optically pure or optically enriched sulfoxides, including **amorphous esomeprazole** and salts thereof, via resolution using transition metal complexes)

IT 87-91-2, Diethyl L-tartrate 121-44-8, Triethylamine, reactions 497-19-8, Sodium carbonate, reactions 546-68-9, Titanium tetraisopropoxide 611-71-2, D-Mandelic acid 1310-58-3, Potassium hydroxide, reactions 1310-73-2, Sodium hydroxide, reactions 7087-68-5, Diisopropylethylamine 7439-95-4, Magnesium, reactions 13811-71-7, Diethyl D-tartrate 17199-29-0, L-Mandelic acid
RL: RGT (Reagent); RACT (Reactant or reagent)
(process for preparation of optically pure or optically enriched sulfoxides, including **amorphous esomeprazole** and salts thereof, via resolution using transition metal complexes)

L3 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1998:479525 CAPLUS
DN 129:86005
TI Crystalline forms of **S-omeprazole**
IN Bohlin, Martin; Horvath, Karol; Von Unge, Sverker
PA Astra AB, Swed.
SO PCT Int. Appl., 24 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9828294	A1	19980702	WO 1997-SE2125	19971216

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

				SE 1996-4793	A	19961220
SE 9604793	A	19980621		SE 1996-4793		19961220
SE 510666	C2	19990614				
TW 538039	B	20030621		TW 1997-86118449		19971208
				SE 1996-4793	A	19961220
ZA 9711046	A	19980622		ZA 1997-11046		19971209
				SE 1996-4793	A	19961220
CA 2274076	AA	19980702		CA 1997-2274076		19971216
				SE 1996-4793	A	19961220
				WO 1997-SE2125	W	19971216
AU 9855026	A1	19980717		AU 1998-55026		19971216
AU 730129	B2	20010222				
				SE 1996-4793	A	19961220
				WO 1997-SE2125	W	19971216
EP 946547	A1	19991006		EP 1997-951367		19971216
EP 946547	B1	20030409				

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

				SE 1996-4793	A	19961220
				WO 1997-SE2125	W	19971216
CN 1241183	A	20000112		CN 1997-180849		19971216
CN 1109684	B	20030528				
				WO 1997-SE2125	W	19971216
EE 9900259	A	20000215		EE 1999-259		19971216
EE 3923	B1	20021216				
				SE 1996-4793	A	19961220
				WO 1997-SE2125	W	19971216
BR 9714059	A	20000509		BR 1997-14059		19971216
				SE 1996-4793	A	19961220
				WO 1997-SE2125	W	19971216
NZ 336024	A	20010223		NZ 1997-336024		19971216
				SE 1996-4793	A	19961220
				WO 1997-SE2125	W	19971216
JP 2001507025	T2	20010529		JP 1998-528685		19971216
				SE 1996-4793	A	19961220
				WO 1997-SE2125	W	19971216
RU 2184734	C2	20020710		RU 1999-116303		19971216
				SE 1996-4793	A	19961220
				WO 1997-SE2125	W	19971216
AT 236898	E	20030415		AT 1997-951367		19971216
				SE 1996-4793	A	19961220
				WO 1997-SE2125	W	19971216
PT 946547	T	20030731		PT 1997-951367		19971216
				SE 1996-4793	A	19961220
ES 2194231	T3	20031116		ES 1997-951367		19971216
				SE 1996-4793	A	19961220
CZ 294784	B6	20050316		CZ 1999-2202		19971216
				SE 1996-4793	A	19961220
US 6162816	A	20001219		US 1998-154		19980128
				SE 1996-4793	A	19961220
				WO 1997-SE2125	W	19971216
MX 9905661	A	20000131		MX 1999-5661		19990617
				SE 1996-4793	A	19961220
				WO 1997-SE2125	W	19971216

NO 9903068	A	19990621	NO 1999-3068		19990621
			SE 1996-4793	A	19961220
			WO 1997-SE2125	W	19971216
HK 1022909	A1	20030911	HK 2000-101986		20000331
			SE 1996-4793	A	19961220
			WO 1997-SE2125	W	19971216

AB **S-omeprazole** is obtained in a partially crystalline and in a substantially crystalline form by recrystn. of the **amorphous** base from an organic solvent. Thus, **S-omeprazole** was obtained from its Na salt by extraction from aqueous solution and evaporation The resulting **amorphous S-omeprazole** was recrystd. from EtOAc to give the partially crystalline form whose x-ray diffraction pattern is reported. The more highly crystalline form was obtained by recrystn. from aqueous acetone.

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Crystalline forms of **S-omeprazole**

AB **S-omeprazole** is obtained in a partially crystalline and in a substantially crystalline form by recrystn. of the **amorphous** base from an organic solvent. Thus, **S-omeprazole** was obtained from its Na salt by extraction from aqueous solution and evaporation The resulting **amorphous S-omeprazole** was recrystd. from EtOAc to give the partially crystalline form whose x-ray diffraction pattern is reported. The more highly crystalline form was obtained by recrystn. from aqueous acetone.

IT Crystallization
(crystalline forms of **S-omeprazole**)

IT 67-64-1, Acetone, uses 75-05-8, Acetonitrile, uses 75-09-2, Methylene chloride, uses 108-88-3, Toluene, uses 141-78-6, Ethyl acetate, uses 7732-18-5, Water, uses
RL: NUU (Other use, unclassified); USES (Uses)
(crystalline forms of **S-omeprazole**)

IT 119141-88-7P, **S-Omeprazole**
RL: PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)
(crystalline forms of **S-omeprazole**)

IT 161796-78-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(crystalline forms of **S-omeprazole**)

=> => file uspatfull
FILE 'USPATFULL' ENTERED AT 12:13:50 ON 21 APR 2005
CA INDEXING COPYRIGHT (C) 2005 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 19 Apr 2005 (20050419/PD)
FILE LAST UPDATED: 19 Apr 2005 (20050419/ED)
HIGHEST GRANTED PATENT NUMBER: US6883176
HIGHEST APPLICATION PUBLICATION NUMBER: US2005081271
CA INDEXING IS CURRENT THROUGH 19 Apr 2005 (20050419/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 19 Apr 2005 (20050419/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Feb 2005
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Feb 2005

>>> USPAT2 is now available. USPATFULL contains full text of the <<<
>>> original, i.e., the earliest published granted patents or <<<
>>> applications. USPAT2 contains full text of the latest US <<<
>>> publications, starting in 2001, for the inventions covered in <<<
>>> USPATFULL. A USPATFULL record contains not only the original <<<

>>> published document but also a list of any subsequent <<<
>>> publications. The publication number, patent kind code, and <<<
>>> publication date for all the US publications for an invention <<<
>>> are displayed in the PI (Patent Information) field of USPATFULL <<<
>>> records and may be searched in standard search fields, e.g., /PN, <<<
>>> /PK, etc. <<<

>>> USPATFULL and USPAT2 can be accessed and searched together <<<
>>> through the new cluster USPATALL. Type FILE USPATALL to <<<
>>> enter this cluster. <<<
>>> <<<
>>> Use USPATALL when searching terms such as patent assignees, <<<
>>> classifications, or claims, that may potentially change from <<<
>>> the earliest to the latest publication. <<<

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d que
L6 2 SEA ESOMEPRAZOLE(W) SALT#

=> d l6 ibib abs hit

L6 ANSWER 1 OF 2 USPATFULL on STN
ACCESSION NUMBER: 2004:307966 USPATFULL
TITLE: Crystalline esomeprazole compounds and process for the preparation thereof
INVENTOR(S): Reddy, Manne Satyanarayana, Hyderabad, INDIA
Kumar, Muppa Kishore, Hyderabad, INDIA
Purandhar, Koilkonda, Hyderabad, INDIA
Reddy, Lekkala Amarnath, Hyderabad, INDIA
PATENT ASSIGNEE(S): DR. REDDY'S LABORATORIES LIMITED (non-U.S. corporation)
DR. REDDY'S LABORATORIES, INC. (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004242642	A1	20041202
APPLICATION INFO.:	US 2003-716200	A1	20031118 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	IN 2002-8522002	20021118

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Ladas & Parry, 26 West 61 Street, New York, NY, 10023
NUMBER OF CLAIMS: 35
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 1 Drawing Page(s)
LINE COUNT: 836
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to crystalline form II of esomeprazole trihydrate and methods of its preparation and use. Preferably, the crystalline form II of esomeprazole trihydrate has an X-ray powder diffraction pattern that includes five or more peaks with 2 theta angles of 4.82±0.09, 5.55±0.09, 7.41±0.09, 8.60±09, 12.10±0.09, 14.16±0.09, 18.47±0.09, and 21.08±0.09.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM [0002] The present invention relates to a crystalline form of hydrated **esomeprazole salt** and in particular to esomeprazole magnesium trihydrate salt, chemically known as (S)(-)5-methoxy-2-[[(4-

methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulphinyl]-1H-benzimidazole trihydrate.

=> d l6 2 ibib abs hit

L6 ANSWER 2 OF 2 USPATFULL on STN

		NUMBER	KIND	DATE
PATENT INFORMATION:		US 2004235903	A1	20041125
APPLICATION INFO.:		US 2003-690897	A1	20031022 (10)
		NUMBER		DATE
PRIORITY INFORMATION:		IN 2002-10572002		20021022

ACCESSION NUMBER: 2004:300034 USPATFULL
TITLE: Amorphous form of **esomeprazole salts**
INVENTOR(S): Khanna, Mahavir Singh, New Delhi, INDIA
Vijayaraghavan, Bakthavathsalan, Gurgaon, INDIA
Prasad, Mohan, Gurgaon, INDIA
Kumar, Yatendra, Gurgaon, INDIA

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: RANBAXY INC., 600 COLLEGE ROAD EAST, SUITE 2100, PRINCETON, NJ, 08540
NUMBER OF CLAIMS: 38
EXEMPLARY CLAIM: 1
LINE COUNT: 374
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention relates to an amorphous form of the salts of the (-) enantiomer or (S)-enantiomer of omeprazole, i.e., esomeprazole. The invention also relates to processes for preparing amorphous **esomeprazole salts** and pharmaceutical compositions that include the amorphous **esomeprazole salts.**

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Amorphous form of **esomeprazole salts**

AB The invention relates to an amorphous form of the salts of the (-) enantiomer or (S)-enantiomer of omeprazole, i.e., esomeprazole. The invention also relates to processes for preparing amorphous **esomeprazole salts** and pharmaceutical compositions that include the amorphous **esomeprazole salts.**

SUMM [0001] The field of the invention relates to an amorphous form of the salts of the (-) enantiomer or (S)-enantiomer of omeprazole, i.e., esomeprazole. The invention also relates to processes for preparing amorphous **esomeprazole salts** and pharmaceutical compositions that include the amorphous **esomeprazole salts.**

SUMM [0008] U.S. Pat. No. 6,124,464 discloses another process for preparing crystalline esomeprazole magnesium. U.S. Pat. No. 6,369,085 discloses three different types of crystalline esomeprazole magnesium viz. dihydrate form A, dihydrate form B and the trihydrate form. However, the inventors are not aware of any disclosure of an amorphous form of **esomeprazole salts**, including amorphous esomeprazole magnesium, in the prior art. It is known that different morphs of biologically active compounds may have different absorption profile in vivo and consequently different pharmacokinetic profile.

DETD [0026] The mentors have found a new form of **esomeprazole**

salts, the amorphous form and, in particular, the amorphous esomeprazole magnesium salt. The new form is characterized by its X-ray powder diffraction pattern and IR spectra as shown in FIGS. 1 and 2, respectively. The inventors also have developed a process for the preparation of the amorphous form of **esomeprazole salts**, including the esomeprazole magnesium salt, by recovering the amorphous **esomeprazole salt** from a solution thereof in a suitable solvent by spray drying. The resulting amorphous form of salts of esomeprazole include, for example, Na, Mg, Li, K, Ca, and N(R).sub.4, where R is hydrogen or an alkyl group with 1-4 carbon atoms. The inventors also have developed pharmaceutical compositions that contain the amorphous form of the **esomeprazole salts**, including the esomeprazole magnesium salt, in admixture with one or more solid or liquid pharmaceutical diluents, carriers, and/or excipients. These pharmaceutical compositions may be used for the treatment of gastric acid-related diseases by inhibition of gastric acid secretion.

DETD [0027] In general, the solution of **esomeprazole salt** may be obtained by dissolving a crystalline **esomeprazole salt** in a suitable solvent. Alternatively, such a solution may be obtained directly from a reaction in which **esomeprazole salt** is formed. The solvent may be removed from the solution by a technique which includes, for example, distillation, distillation under vacuum, evaporation, spray drying, and freeze drying.

DETD [0030] The term "suitable solvent" includes any solvent or solvent mixture in which **esomeprazole salt**, including esomeprazole magnesium, is soluble, including, for example, nitriles, cyclic ethers, lower alkanol, ketones, esters, chlorinated solvents, acetonitrile and mixtures thereof. Examples of alcohols include methanol, ethanol, isopropanol, and the like. Examples of halogenated hydrocarbons include dichloromethane, dichloroethane, dibromoethane, and the like. Examples of nitrile include acetonitrile and the like. Examples of cyclic ethers include tetrahydrofuran, dioxane, and the like. Examples of alkanol include those primary, secondary and tertiary alcohols having from one to six carbon atoms. Suitable lower alkanol solvents include methanol, ethanol, denatured spirit, n-propanol, isopropanol, n-butanol, isobutanol and t-butanol. Examples of ketones or esters include solvents such as acetone, 2-butanone, 4-methylpentan-2-one, ethyl acetate and n-butylacetate. A suitable chlorinated solvent includes one or both of dichloromethane and chloroform. Mixtures of all of these solvents are also contemplated.

DETD [0031] An organic amine or ammonia may optionally be added to the solution of **esomeprazole salt**, including esomeprazole magnesium, before spray drying. The organic amine may be one or more of diethylamine, triethylamine, and the like. One purpose of adding the organic amine or ammonia is to provide stability to the esomprazole during processing.

DETD [0034] The resulting amorphous form of **esomeprazole salt** and, in particular, esomeprazole magnesium, may be formulated into ordinary dosage forms such as, for example, tablets, capsules, pills, solutions, etc. In these cases, the medicaments can be prepared by conventional methods with conventional pharmaceutical excipients. In addition to the common dosage forms set out above, the amorphous form of esomeprazole magnesium may also be administered by controlled release means and/or delivery devices.

DETD [0035] Further, the amorphous **esomeprazole salt** dosage forms described herein can be used in a method for treatment of gastric acid related diseases. The method of treatment includes administering to a mammal in need of treatment a dosage form that includes a therapeutically effective amount of the amorphous form of **esomeprazole salt**, including the esomeprazole magnesium salt.

CLM What is claimed is:

7. The amorphous form of a salt of esomeprazole of claim 1, wherein the **esomeprazole salt** has the X-ray diffraction pattern of a plain halo.

15. The pharmaceutical composition of claim 10, wherein the **esomeprazole salt** has the X-ray diffraction pattern of a plain halo of FIG. 1.

37. The process of claim 17, wherein the amorphous **esomeprazole salt** obtained has the X-ray diffraction pattern of a plain halo.

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=> file uspatall
FILE 'USPATFULL' ENTERED AT 12:28:17 ON 21 APR 2005
CA INDEXING COPYRIGHT (C) 2005 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'USPAT2' ENTERED AT 12:28:17 ON 21 APR 2005
CA INDEXING COPYRIGHT (C) 2005 AMERICAN CHEMICAL SOCIETY (ACS)

=> d que
L1          187 SEA FILE=USPATFULL (S(W)OMEPRAZOLE OR ESOMEPRAZOLE)
L2           42 SEA FILE=USPATFULL L1 AND AMORPHOUS


=> d l2  1-42 ibib abs hit

L2   ANSWER 1 OF 42  USPATFULL on STN
ACCESSION NUMBER:        2005:87904  USPATFULL
TITLE:                   Novel form of S-omeprazole
INVENTOR(S):             Cotton, Hanna, Sodertalje, SWEDEN
                         Kronstrom, Anders, Sodertalje, SWEDEN
                         Mattson, Anders, Sodertalje, SWEDEN
                         Moller, Eva, Sodertalje, SWEDEN

                              NUMBER        KIND    DATE
                         --------------- ------ --------
PATENT INFORMATION:      US 2005075369      A1   20050407
APPLICATION INFO.:       US 2003-672936     A1   20030925  (10)
RELATED APPLN. INFO.:    Continuation of Ser. No. US 2002-76711, filed on 14 Feb
                         2002, GRANTED, Pat. No. US 6677455 Division of Ser. No.
                         US 1998-77719, filed on 8 Jun 1998, GRANTED, Pat. No.
                         US 6369085 A 371 of International Ser. No. WO
                         1998-SE974, filed on 25 May 1998, UNKNOWN

                               NUMBER        DATE
                         ----------------- --------
PRIORITY INFORMATION:    SE 1997-2065       19970530
DOCUMENT TYPE:           Utility
FILE SEGMENT:            APPLICATION
LEGAL REPRESENTATIVE:    WHITE & CASE LLP, PATENT DEPARTMENT, 1155 AVENUE OF THE
                         AMERICAS, NEW YORK, NY, 10036
NUMBER OF CLAIMS:        7
EXEMPLARY CLAIM:         1
NUMBER OF DRAWINGS:      5 Drawing Page(s)
LINE COUNT:              508
AB       The present invention relates to a novel form of the (-)-enantiomer of
         5-methoxy-2[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-
         benzimidazole, i.e. S-omeprazole. More specifically,
         it relates to a novel form of the magnesium salt of the S-enantiomer of
         omeprazole trihydrate. The present invention also relates to processes
         for preparing such a form of the magnesium salt of S-
         omeprazole and pharmaceutical compositions containing it.
         Furthermore, the present invention also relates to new intermediates
         used in the process.

TI       Novel form of S-omeprazole
AB       The present invention relates to a novel form of the (-)-enantiomer of
         5-methoxy-2[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-
         benzimidazole, i.e. S-omeprazole. More specifically,
         it relates to a novel form of the magnesium salt of the S-enantiomer of
         omeprazole trihydrate. The present invention also relates to processes
         for preparing such a form of the magnesium salt of S-
         omeprazole and pharmaceutical compositions containing it.
         Furthermore, the present invention also relates to new intermediates
```

used in the process.

SUMM [0001] The present invention relates to a novel form of the (-)-enantiomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole, i.e. **S-omeprazole**. More specifically, it relates to a novel form of the magnesium salt of the S-enantiomer of omeprazole trihydrate. The present invention also relates to processes for preparing such a form of the magnesium salt of **S-omeprazole** and pharmaceutical compositions containing it. Furthermore, the present invention also relates to intermediates used in the process, and their preparation.

SUMM [0003] Omeprazole is a sulfoxide and a chiral compound, wherein the sulfur atom being the stereogenic center. Thus, omeprazole is a racemic mixture of its two single enantiomers, the R and S-enantiomer of omeprazole, herein referred to as R-omeprazole and **S-omeprazole.** The absolute configurations of the enantiomers of omeprazole have been determined by an X-ray study of an N-alkylated derivative of the (+)-enantiomer in non-salt form. The (+)-enantiomer of the non-salt form and the (-)-enantiomer of the non-salt form were found to have R and S configuration, respectively, and the (+)-enantiomer of the magnesium salt and the (-)-enantiomer of the magnesium salt were also found to have R and S configuration, respectively. The conditions for the optical rotation measurement for each of these enantiomers are described in WO 94/27988.

SUMM [0005] WO 96/02535 discloses a process for the preparation of the single enantiomers of omeprazole and salts thereof, and WO 96/01623 discloses a suitable tableted dosage forms of for instance magnesium salts of R- and **S-omeprazole.**

DRWD [0006] FIG. 1 shows a X-ray powder diffractogram of the magnesium salt of **S-omeprazole** trihydrate prepared according to the present invention.

DRWD [0007] FIG. 2 shows a X-ray powder diffractogram of the potassium salt of **S-omeprazole** prepared and used in the present application (See examples 2 and 3)

DRWD [0008] FIG. 3 shows a X-ray powder diffractogram of a magnesium salt of **S-omeprazole** dihydrate prepared and used in the present application (See example 5)

DRWD [0009] FIG. 4 shows a X-ray powder diffractogram of a magnesium salt of **S-omeprazole** dihydrate which is a polymorph of the dihydrate shown in FIG. 3 (See Example 6). This magnesium salt of **S-omeprazole** dihydrate has been prepared and can be used in the preparation of the magnesium salt of **S-omeprazole** trihydrate according to the present invention.

DRWD [0010] FIG. 5 shows X-ray powder diffractogram of the magnesium salt of **S-omeprazole** prepared according to example A in WO 96/01623.

DETD [0011] It has surprisingly been found that the magnesium salt of **S-omeprazole** occurs in a number of structurally different forms. It is an object of the present invention to provide a substantially pure magnesium salt of **S-omeprazole** trihydrate, hereinafter referred to as the compound of the invention. This trihydrate can be obtained as a well defined compound. The present invention also provides a process to obtain and a method of differentiating the magnesium salt of **S-omeprazole** trihydrate from other forms of magnesium salts of **S-omeprazole.**

DETD [0013] The magnesium salt of **S-omeprazole** trihydrate obtained according to the present invention is substantially free from magnesium salts of R-omeprazole. The magnesium salt of **S-omeprazole** trihydrate obtained according to the present

invention is also substantially free from other forms of magnesium salts of **S-omeprazole**, such as the corresponding magnesium salt compounds described in prior art, and dihydrates used in the preparation of the trihydrate compound according to the present invention.

DETD [0014] The compound of the invention is characterized by the positions and intensities of the major peaks in the X-ray powder diffractogram, but may also be characterized by conventional FT-IR spectroscopy. These characteristics are not exhibited by any other form of magnesium salt of **S-omeprazole** and accordingly, the magnesium salt of **S-omeprazole** trihydrate is easily distinguishable from any other crystal form of the magnesium salt of **S-omeprazole** disclosed in prior art. The compound of the invention is characterized by being highly crystalline, i.e. having a higher crystallinity than any other form of magnesium salt of **S-omeprazole** disclosed in the prior art. With the expression "any other form" is meant anhydrates, hydrates, solvates, and polymorphs or **amorphous** forms thereof disclosed in the prior art. Examples of any other forms of magnesium salt of **S-omeprazole** includes, but are not limited to, anhydrates, monohydrates, dihydrates, sesquihydrates, trihydrates, alcoholates, such as methanolates and ethanolates, and polymorphs or **amorphous** forms thereof.

DETD [0016] In a further aspect, the present invention provides processes for the preparation of the magnesium salt of **S-omeprazole** trihydrate which comprises;

DETD [0017] a) treating a magnesium salt of **S-omeprazole** of any form, for example prepared according is to procedures known in the art such as Example A in WO 96/01623 which is incorporated herein by reference, with water at a suitable temperature for a suitable time. By a suitable temperature is meant a temperature which induces the transformation of starting material to product without decomposing any of these compounds. Examples of such suitable temperatures include, but are not limited to, room temperature and above. By a suitable time is meant a time that results in high conversion of the starting material into product without causing any decomposition of either compounds, i.e. results in a good yield. This suitable time will vary depending on the temperature used in a way well known to people in the art. The higher the temperature, the shorter time is needed to give the desired conversion. The amount of water is not crucial and will depend on the process conditions used. The magnesium salt of **S-omeprazole** trihydrate is thereafter separated from the aqueous slurry, for example by filtration or centrifugation and thereafter dried to constant weight; or

DETD [0020] The resulting potassium salt of **S-omeprazole** is thereafter converted to the corresponding magnesium salt by treatment with a magnesium source, such as magnesium sulfate in a lower alcohol, such as methanol. The solution is optionally filtered and the precipitation is initialized by addition of a non-solvent such as acetone. The product is filtered off and optionally washed with water and further processed as is described in a) above. Alternatively, the potassium salt may be treated with a magnesium source, such as magnesium sulfate in water, and isolation of the magnesium salt of **S-omeprazole** trihydrate, or any other conventional technique for transforming a potassium salt to the corresponding magnesium salt can be used and is within the scope of the present invention.

DETD [0021] Yet a further aspect of the present invention is to provide a suitable intermediate used in the preparation of the compound of the invention, as well as a process for its preparation. The potassium salt of **S-omeprazole** is found to be such a suitable intermediate. The potassium salt of **S-omeprazole** may also be used as an active component of a pharmaceutical formulation to be used in the treatment of gastrointestinal diseases.

DETD [0022] The compound of the invention, i.e. the magnesium salt of **S-omeprazole** trihydrate, prepared according to the present invention may be analyzed by XRPD, a technique which is known per se.

DETD [0023] The amount of water in the magnesium salt of **S-omeprazole** trihydrate is determined by thermogravimetric analysis, a technique which is known per se.

DETD [0025] Any suitable route of administration may be employed for providing the patient with an effective dosage of the magnesium salt of **S-omeprazole** trihydrate, according to the invention. For example, peroral or parental formulations and the like may be employed. Dosage forms include capsules, tablets, dispersions, suspensions and the like.

DETD [0026] It is further provided a pharmaceutical composition comprising the magnesium salt of **S-omeprazole** trihydrate according to the invention, as active ingredient, in association with a pharmaceutically acceptable carrier, diluent or excipient and optionally other therapeutic ingredients. Compositions comprising other therapeutic ingredients are especially of interest in the treatment of Helicobacter infections. The invention also provides the use of the magnesium salt of **S-omeprazole** trihydrate of the invention in the manufacture of a medicament for use in the treatment of a gastric-acid related condition and a method of treating a gastric-acid related condition which method comprises administering to a subject suffering from said condition a therapeutically effective amount of the magnesium salt of **S-omeprazole** trihydrate according to the invention.

DETD [0028] In the practice of the invention, the most suitable route of administration as well as the magnitude of a therapeutic dose of the magnesium salt of **S-omeprazole** trihydrate according to the invention in any given case will depend on the nature and severity of the disease to be treated. The dose, and dose frequency, may also vary according to the age, body weight, and response of the individual patient. Special requirements may be needed for patients having Zollinger-Ellison syndrome, such as a need for higher doses than the average patient. Children and patients with liver diseases generally will benefit from doses that are somewhat lower than the average. Thus, in some conditions it may be necessary to use doses outside the ranges stated below, for example long term treatments may request lower dosage. Such higher and lower doses are within the scope of the present invention. Such daily doses may vary between 5 mg to 300 mg.

DETD [0031] Combination preparations comprising the magnesium salt of **S-omeprazole** trihydrate and other active ingredients may also be used. Examples of such active ingredients include, but are not limited to anti-bacterial compounds, non-steroidal anti-inflammatory agents, antacid agents, alginates and prokinetic agents.

DETD [0033] Water (157 kg) was added to the wet crystals of the magnesium salt of **S-omeprazole**, prepared according to Example 4, below. The mixture was heated to 38° C. with stirring and left for 3 hours. The crystals were filtered off and dried in vacuo. Yield: 31.6 kg.

DETD [0035] Some additional very weak peaks found in the diffractogram have been omitted from table 1.

TABLE 1

Positions and intensities of the major peaks in the XRP-diffractogram of the magnesium salt of **S-omeprazole** trihydrate.

d-value/Å	Relative Intensity
2.67	m
2.79	m

3.27	m
3.52	s
3.82	s
3.96	vs
4.14	m
5.2	m
5.6	m
6.7	vs
6.9	s
8.3	w
16.6	vs

DETD [0040] The products from Examples 2 and 3 were analysed using X-ray powder diffraction as described in Example 1 and gave the diffractogram depicted in FIG. 2 and given below in Table 2. Some additional very weak peaks found in the diffractogram have been omitted from Table 2.

TABLE 2

Positions and intensities of the major peaks in the XRP-diffractogram of the potassium salt of **S-omeprazole.**

d-value/Å	Relative intensity
13.6	vs
10.6	vw
7.8	m
6.8	m
6.5	m
6.2	w
6.1	m
5.8	s
5.4	m
5.3	w
5.2	w
5.0	vw
4.75	m
4.71	w
4.52	w
4.42	w
4.32	w
4.27	m
3.98	vw
3.92	w
3.89	w
3.87	w
3.81	w
3.74	m
3.60	m
3.55	m
3.52	m
3.42	w
3.38	w
3.34	m
3.28	w
3.20	m
3.12	w
3.06	w
3.03	w
2.97	w
2.93	vw
2.89	w
2.85	m

2.76	w
2.71	vw
2.66	vw
2.58	w
2.57	w
2.56	w
2.52	vw
2.47	vw
2.45	vw
2.43	vw
2.40	vw
2.38	vw
2.31	vw

$\alpha 1$ = 1.54060 Å

DETD [0043] The product was analyzed using X-ray powder diffraction as described in Example 1, and the analyze gave the diffractogram depicted in FIG. 3 and given below in Table 3. Some additional peaks with low intensities found in the diffractogram have been omitted from Table 3.

TABLE 3

Positions and intensities of the major peaks in the XRP-diffractogram of the magnesium salt of **S-omeprazole** dihydrate, Form B.

d-value/Å	Relative Intensity
4.19	m
4.45	m
4.68	m
4.79	s
4.91	s
4.98	s
5.1	m
5.4	s
5.5	m
5.6	m
5.8	m
6.3	m
6.7	s
7.9	m
8.1	s
11.0	m
11.8	m
14.9	vs

DETD [0044] Convention of Magnesium Salt of **S-omeprazole** Dehydrate to Trihydrate

DETD [0047] The product was analyzed using X-ray powder diffration as described in Example 1 and gave the diffractogram depicted in FIG. 4 and given below in Table 4. Some additional peaks with low intensities found in the diffractogram have been omitted from Table 4.

TABLE 4

Positions and intensities of the major peaks in the XRP-diffractogram of the magnesium salt of **S-omeprazole** dihydrate, Form A.

d-value/Å	Relative Intensity
3.04	s
3.14	s
3.18	m
4.05	s
4.19	s

4.32	m
4.54	s
4.69	vs
5.2	s
5.3	s
5.8	s
6.2	vs
6.6	s
15.5	vs

CLM What is claimed is:

1. The magnesium salt of **S-omeprazole** trihydrate.

2. The magnesium salt of **S-omeprazole** trihydrate according to claim 1, wherein the compound is in a highly crystalline form.

14. A pharmaceutical composition comprising the magnesium salt of **S-omeprazole** trihydrate according to claim 1 or 2 as active ingredient in association with a pharmaceutically acceptable carrier.

18. A method of treating a gastric acid related condition which method comprises administering to a subject suffering from said condition a therapeutically effective amount of the magnesium salt of **S-omeprazole** trihydrate according to claim 1 or 2.

L2 ANSWER 2 OF 42 USPATFULL on STN

ACCESSION NUMBER:	2005:69524 USPATFULL
TITLE:	Substituted aryl compounds as novel cyclooxygenase-2 selective inhibitors, compositions and methods of use
INVENTOR(S):	Khanapure, Subhash P., Clinton, MA, UNITED STATES Garvey, David S., Dover, MA, UNITED STATES Earl, Richard A., Westford, MA, UNITED STATES Ezawa, Maiko, Acton, MA, UNITED STATES Fang, Xinqin, Lexington, MA, UNITED STATES Gaston, Ricky D., Malden, MA, UNITED STATES
PATENT ASSIGNEE(S):	NitroMed, Inc., Lexington, MA (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2005059665	A1	20050317
APPLICATION INFO.:	US 2004-969079	A1	20041021 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2003-730979, filed on 10 Dec 2003, GRANTED, Pat. No. US 6825185 Division of Ser. No. US 2001-24046, filed on 21 Dec 2001, GRANTED, Pat. No. US 6706724

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-256932P	20001221 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	WILMER CUTLER PICKERING HALE AND DORR LLP, THE WILLARD OFFICE BUILDING, 1455 PENNSYLVANIA AVE, NW, WASHINGTON, DC, 20004
NUMBER OF CLAIMS:	21
EXEMPLARY CLAIM:	1
LINE COUNT:	4603

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention describes novel substituted aryl compounds that are cyclooxygenase 2 (COX-2) selective inhibitors and novel compositions

comprising at least one cyclooxygenase 2 (COX-2) selective inhibitor, and, optionally, at least one compound that donates, transfers or releases nitric oxide, stimulates endogenous synthesis of nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor or is a substrate for nitric oxide synthase, and/or, optionally, at least one therapeutic agent, such as, steroids, nonsterodal anti-inflammatory compounds (NSAID), 5-lipoxygenase (5-LO) inhibitors, leukotriene B.sub.4 (LTB.sub.4) receptor antagonists, leukotriene A.sub.4 (LTA.sub.4) hydrolase inhibitors, 5-HT agonists, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) inhibitors, H.sub.2 antagonists, antineoplastic agents, antiplatelet agents, thrombin inhibitors, thromboxane inhibitors, decongestants, diuretics, sedating or non-sedating anti-histamines, inducible nitric oxide synthase inhibitors, opioids, analgesics, Helicobacter pylori inhibitors, proton-pump-inhibitors, isoprostane inhibitors, and mixtures thereof. The invention also provides novel kits comprising at least one COX-2 selective inhibitor, and, optionally, at least one nitric oxide donor, and/or, optionally, at least one therapeutic agent. The novel cyclooxygenase 2 selective inhibitors of the invention can be optionally nitrosated and/or nitrosylated. The invention also provides methods for treating inflammation, pain and fever; for treating and/or improving the gastrointestinal properties of COX-2 selective inhibitors; for facilitating wound healing; for treating and/or preventing renal toxicity or other toxicities; for treating and/or preventing other disorders resulting from elevated levels of cyclooxygenase-2; and for improving the cardiovascular profile of COX-2 selective inhibitors.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD [0522] Suitable proton pump inhibitors, include, but are not limited to, omeprazole, **esomeprazole**, lansoprazole, rabeprazole, pantoprazole, and the like. Suitable proton pump inhibitors are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995, Pgs. 901-915; the Merck Index on CD-ROM, Twelfth Edition, Version 12:1, 1996; and in WO 00/50037 assigned to NitroMed Inc., the disclosures of which are incorporated herein by reference in their entirety.

DETD [0685] To acetic anhydride (0.460 mL) at 0° C. was added drop-wise, with stirring, fuming nitric acid (0.140 mL). This mixture was immediately added drop-wise to a solution of the product of Example 18b (0.43 mmol, 0.216 g) dissolved in ethyl acetate (5 mL), at 0° C. The resulting solution was stirred at 0° C. for 30 min, then quenched with water and neutralized with sodium carbonate. The organic layer was separated, dried over magnesium sulfate and filtered. The filtrate was evaporated under reduced pressure. Purification by silica gel column chromatography using ethyl acetate as the eluant gave the title compound as an **amorphous** glassy solid (0.217 g, 92% yield). .sup.1H NMR (300 MHz, CDCl.sub.3) δ7.95 (d, J=8.0 Hz, 2H), 7.39 (d, J=8.0 Hz, 2H), 6.88 (m, 3H), 6.61 (t, J=8.8 Hz, 1H), 6.43 (m, 2H), 4.79 (m, 1H), 4.61 (m, 3H), 4.28 (dd, J=7.3, 11.4 Hz, 1H), 3.83 (s, 2H), 3.12 (s, 3H); MS (APIMS) m/e 503 (M+H-NO2).sup.+, 566 (M+18).sup.+.

DETD [0689] To acetic anhydride (0.230 mL) at 0° C. was added drop-wise, with stirring, fuming nitric acid (0.07 mL). This mixture was immediately added drop-wise to a solution of the product of Example 19a (0.25 mmol, 0.112 g) dissolved in ethyl acetate, at 0° C. The resulting solution was stirred at 0° C. for 15 min, then quenched with water and neutralized with sodium carbonate. The organic layer was separated, dried over magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure. Purification by silica gel column chromatography using ethyl acetate as the eluant gave the title compound as an **amorphous** glassy solid, (69 mg, 56% yield). .sup.1H NMR (300 MHz, CDCl.sub.3) δ7.91 (d, J=8.3 Hz, 2H), 7.35 (d, J=8.3 Hz,

2H), 6.81 (s, 0.5H), 6.80 (s, 0.5H), 6.79 (s, 0.5H), 6.78 (s, 0.5H), 6.59 (tt, J=2.3, 9.0 Hz, 1H), 6.41 (m, 2H), 4.73 (m, 2H), 4.57 (m, 1H), 4.35 (m, 1H), 4.18 (dd, J=3.2, 6.2 Hz, 0.5H), 4.14 (dd, J=3.2, 6.2 Hz, 0.5H), 3.79 (s, 2H), 3.09 (s, 3H); MS (APIMS) m/e 509 (M+18).sup.+.

L2 ANSWER 3 OF 42 USPATFULL on STN

ACCESSION NUMBER: 2005:49485 USPATFULL

TITLE: Pharmaceutical compositions having a swellable coating

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	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2005042277	A1	20050224	
APPLICATION INFO.:	US 2004-893563	A1	20040716	(10)

	NUMBER	DATE	
PRIORITY INFORMATION:	IN 2003-5802003	20030717	
	IN 2003-10642003	20031230	
	US 2004-563707P	20040420	(60)

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION

LEGAL REPRESENTATIVE: Robert A. Franks, Dr. Reddy's Laboratories, Inc., Seventh Floor, 200 Somerset Corporate Boulevard, Bridgewater, NJ, 08807

NUMBER OF CLAIMS: 37

EXEMPLARY CLAIM: 1

LINE COUNT: 1060

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A pharmaceutical dosage form containing a pharmaceutical active that is not stable in the presence of acid comprises a core containing the active and a disintegrant, a swellable coating surrounding the core, and an enteric coating surrounding the swellable coating.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD [0024] In this application, the terms "pharmaceutical active ingredient" "pharmaceutical active" and "active" are used interchangeably to refer to a component of a pharmaceutical dosage form that provides a therapeutic effect upon administration to a subject. This invention is particularly applicable to acid-sensitive pharmaceutical actives, which exhibit instability in a low-pH environment, such as the benzimidazole derivatives, including their optically active isomers. Specific examples of useful benzimidazole compounds include rabeprazole, omeprazole, **esomeprazole**, lansoprazole, and pantoprazole. Other drugs for which the invention will be useful include, without limitation thereto: pharmaceutical actives that react with enteric coating components, examples being drugs that form insoluble complexes with the enteric coatings, such as fluoxetine and duloxetine; and highly alkaline drugs that can react with acidic groups to reduce the acid-insolubility of the coating, such as diclofenac sodium and piroxicam.

DETD [0026] Generally, the swellable coating, upon wetting, becomes a hydrocolloid, which is a gelatinous suspension of microscopic particles in water. Preferably, the hydrocolloid is formed from a prolamine, such as gliadan, hordein, or, more preferably, zein. Zein is extracted from corn as a granular, straw to pale yellow colored **amorphous**

powder or fine flakes and various commercial extracts have molecular weights in the range of 25,000-35,000. Zein is insoluble in water and insoluble in alcohols, but soluble in aqueous alcohol solutions. Chemically, zein is fairly abundant in glutamine and devoid of lysine and tryptophan. Zein comprises about 20-22% glutamic acid and glutamine, 17-20% leucine, 5-9% proline, 8-10% alanine, 4-7% phenylalanine, 3-7% isoleucine, 4-6% serine, 4-5% asparginine and 3-5% tyrosine. All of the other amino acids in zein each comprise less than 3%. Zein has been generally recognized as safe (GRAS) by the United States Food and Drug Administration since March, 1985 for use in food and pharmaceutical products. Zein is available commercially from several sources, including Freeman Industries LLC, Tuckahoe, N.Y. USA; among the commercial zein products sold by this company are those designated Zein F4000, Zein 4400, Zein F6000, Zein G-10, Aqua Zein, and Aqua Zein Neutral.

DETD [0064] Capsules containing **esomeprazole** were prepared using the following components and procedure:

Ingredients	Quantity (g)
Pellets	
Esomeprazole magnesium trihydrate	178
Mannitol	938
Crospovidone	72
Sodium lauryl sulphate	20
Copovidone	32
Total	1240
Swellable Coating	
Zein	16.2
Sodium lauryl sulphate	1.62
Cum. Total	1257.82
Enteric Coating	
Methacrylic acid copolymer Type C	110
Triethyl citrate	11
Titanium dioxide	15.29
Talc	16.5
Cum. Total	1410.61

DETD [0065] The core was prepared by mixing **esomeprazole** magnesium trihydrate, mannitol, crospovidone and sodium lauryl sulphate and granulating this mixture with an aqueous solution of copovidone. The granules were then subjected to extrusion and spheronization to obtain spherical pellets. The pellets were dried by conventional drying techniques. The dried pellets were coated with intermediate coating solution containing zein and sodium lauryl sulphate dissolved in a mixture of isopropyl alcohol and water, then dried. The enteric coat was prepared by dissolving Methacrylic Acid Copolymer Type C and triethyl citrate in isopropyl alcohol and dispersing talc and titanium dioxide in this solution.

DETD [0066] Coated pellets are filled into gelatin capsules, giving 4000 capsules that each contain 40 mg of **esomeprazole**.

DETD [0067] **Esomeprazole** tablets were prepared, using the following ingredients and procedure.

Ingredients	Quantity (mg/tablet)
Core Tablet	
Esomeprazole magnesium trihydrate	44.5
Magnesium oxide	20
Plasdone S-630	17.5

Crospovidone	10
Mannitol (Pearlitol SD 200)	227
Colloidal silicon dioxide	3.5
Sodium stearyl fumarate	17.5
Total	340
Swellable Coating	
Zein F6000	6.8
Cum. Total	346.8
Enteric Coating	
Eudragit L100-55	19.1
Triethyl citrate	1.9
Titanium dioxide	3.8
Talc	2.9
Cum. Total	374.5

DETD [0068] **Esomeprazole** magnesium trihydrate, magnesium oxide, copovidone, crospovidone, mannitol, and silicon dioxide were blended, then sodium stearyl fumarate was added with further blending. This mixture was compressed into core tablets. The tablets were coated with an aqueous alcohol solution of zein, then dried. Finally, the enteric coating ingredients were dispersed in water and coated onto the zein-coated tablets, followed by a final drying.

DETD [0078] **Esomeprazole** tablets were prepared using the following ingredients and the procedure described below.

Ingredients	Quantity/Tablet (mg)
Core Tablet	
Esomeprazole magnesium trihydrate	44.5
Magnesium oxide	20
Plasdone S-630	17.5
Mannitol (Pearlitol SD 200)	237
Colloidal silicon dioxide	3.5
Sodium stearyl fumarate	17.5
Total	340
Swellable Coating	
Zein F6000	6.8
Cum. total	346.8

DETD [0079] **Esomeprazole** magnesium trihydrate, magnesium oxide, Plasdone S-630, silicon dioxide, and mannitol were sieved and blended, then sodium stearyl fumarate was added and the mixture blended, and finally tablets were formed by direct compression of the mixture. Zein was dissolved in aqueous alcohol and coated onto the tablets. The coated tablets were then dried.

CLM What is claimed is:

7. The pharmaceutical dosage form of claim 6, wherein the benzimidazole is one or more members selected from the group consisting of omeprazole, **esomeprazole**, lansoprazole, rabeprazole and pantoprazole.

L2 ANSWER 4 OF 42 USPATFULL on STN

ACCESSION NUMBER: 2005:43344 USPATFULL

TITLE: Pharmaceutical formulatins useful for inhibiting acid secretion and methods for making and using them

INVENTOR(S): Hall, Warren, San Diego, CA, UNITED STATES
Olmstead, Kay, San Diego, CA, UNITED STATES
Weston, Laura, San Diego, CA, UNITED STATES

PATENT ASSIGNEE(S): Santarus, Inc. (U.S. corporation)

NUMBER	KIND	DATE

10/690,897

PATENT INFORMATION: US 2005037070 A1 20050217
APPLICATION INFO.: US 2004-893203 A1 20040716 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2003-488321P	20030718 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: WILSON SONSINI GOODRICH & ROSATI, 650 PAGE MILL ROAD, PALO ALTO, CA, 943041050
NUMBER OF CLAIMS: 55
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 2575
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB In one general aspect of the present invention, pharmaceutical formulations comprising both a proton pump inhibitor microencapsulated with a material that enhances the shelf-life of the pharmaceutical composition and one or more antacid are described. In another general aspect of the present invention, pharmaceutical formulations comprising both a proton pump inhibitor microencapsulated with a taste-masking material and one or more antacid are described.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM [0005] A class of acid-labile pharmaceutical compounds that are administered as enteric-coated dosage forms are proton pump inhibiting agents. Exemplary proton pump inhibitors include, omeprazole (Prilosec®), lansoprazole (Prevacid®), **esomeprazole** (Nexium®), rabeprazole (Aciphex®), pantoprazole (Protonix®), pariprazole, tentaprazole, and leminoprazole. The drugs of this class suppress gastrointestinal acid secretion by the specific inhibition of the H.sup.+/K.sup.+-ATPase enzyme system (proton pump) at the secretory surface of the gastrointestinal parietal cell. Most proton pump inhibitors are susceptible to acid degradation and, as such, are rapidly destroyed as pH falls to an acidic level. Therefore, if the enteric-coating of these formulated products is disrupted (e.g., trituration to compound a liquid, or chewing the capsule or tablet) or the buffering agent fails to sufficiently neutralize the gastrointestinal pH, the drug will be exposed to degradation by the gastrointestinal acid in the stomach.

DETD [0029] "Anti-adherents," "glidants," or "anti-adhesion" agents prevent components of the formulation from aggregating or sticking and improve flow characteristics of a material. Such compounds include, e.g., colloidal silicon dioxide such as Cab-o-sil®; tribasic calcium phosphate, talc, corn starch, DL-leucine, sodium lauryl sulfate, magnesium stearate, calcium stearate, sodium stearate, kaolin, and micronized **amorphous** silicon dioxide (Syloid®) and the like.

DETD [0072] In various embodiments, the proton pump inhibitor can be a substituted bicyclic aryl-imidazole, wherein the aryl group can be, e.g., a pyridine, a phenyl, or a pyrimidine group and is attached to the 4- and 5-positions of the imidazole ring. Proton pump inhibitors comprising a substituted bicyclic aryl-imidazoles include, but are not limited to, omeprazole, hydroxyomeprazole, **esomeprazole**, lansoprazole, pantoprazole, rabeprazole, dontoprazole, habeprazole, perprazole, tenatoprazole, ransoprazole, pariprazole, leminoprazole, or a free base, free acid, salt, hydrate, ester, amide, enantiomer, isomer, tautomer, polymorph, prodrug, or derivative thereof. See, e.g., The Merck Index, Merck & Co. Rahway, N.J. (2001).

DETD [0080] Salt forms of proton pump inhibiting agents include, but are not limited to: a sodium salt form such as **esomeprazole** sodium,

omeprazole sodium, rabeprazole sodium, pantoprazole sodium; or a magnesium salt form such as **esomeprazole** magnesium or omeprazole magnesium, described in U.S. Pat. No. 5,900,424; a calcium salt form; or a potassium salt form such as the potassium salt of **esomeprazole**, described in U.S. Patent Application No. 02/0198239 and U.S. Pat. No. 6,511,996. Other salts of **esomeprazole** are described in U.S. Pat. Nos. 4,738,974 and 6,369,085. Salt forms of pantoprazole and lansoprazole are discussed in U.S. Pat. Nos. 4,758,579 and 4,628,098, respectively.

CLM What is claimed is:

2. A pharmaceutical formulation according to claim 1, wherein the proton pump inhibitor is a substituted bicyclic aryl-imidazole selected from the group consisting of omeprazole, hydroxyomeprazole, **esomeprazole**, tenatoprazole, lansoprazole, pantoprazole, rabeprazole, dontoprazole, habeprazole, perprazole, ransoprazole, pariprazole, leminoprazole; or a free base, free acid, salt, hydrate, ester, amide, enantiomer, isomer, tautomer, polymorph, or prodrug thereof.

3. A pharmaceutical formulation according to claim 1, wherein the proton pump inhibitor is selected from omeprazole, lansoprazole, **esomeprazole**, or a free base, free acid, salt, hydrate, ester, amide, enantiomer, isomer, tautomer, polymorph, or prodrug thereof.

27. A pharmaceutical formulation according to claim 26, wherein the proton pump inhibitor is a substituted bicyclic aryl-imidazole selected from the group consisting of omeprazole, hydroxyomeprazole, **esomeprazole**, tenatoprazole, lansoprazole, pantoprazole, rabeprazole, dontoprazole, habeprazole, perprazole, ransoprazole, pariprazole, leminoprazole; or a free base, free acid, salt, hydrate, ester, amide, enantiomer, isomer, tautomer, polymorph, or prodrug thereof.

28. A pharmaceutical formulation according to claim 26, wherein the proton pump inhibitor is selected from omeprazole, lansoprazole, **esomeprazole**, or a free base, free acid, salt, hydrate, ester, amide, enantiomer, isomer, tautomer, polymorph, or prodrug thereof.

L2 ANSWER 5 OF 42 USPATFULL on STN

ACCESSION NUMBER:	2005:37025 USPATFULL
TITLE:	Pharmaceutical formulation and method for treating acid-caused gastrointestinal disorders
INVENTOR(S):	Hall, Warren, San Diego, CA, UNITED STATES Olmstead, Kay, San Diego, CA, UNITED STATES Weston, Laura, San Diego, CA, UNITED STATES
PATENT ASSIGNEE(S):	Sanatarus, Inc. (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2005031700	A1	20050210	
APPLICATION INFO.:	US 2004-893092	A1	20040716	(10)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 2003-488324P	20030718	(60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	WILSON SONSINI GOODRICH & ROSATI, 650 PAGE MILL ROAD, PALO ALTO, CA, 943041050
NUMBER OF CLAIMS:	43
EXEMPLARY CLAIM:	1

NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 2754
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Pharmaceutical formulations in the form of a powder for suspension comprising at least one proton pump inhibitor in micronized form; at least one antacid; and at lest one suspending agents are provided herein. Also provided herein are methods for making and using pharmaceutical formulations comprising at least one proton pump inhibitor and at least one antacid.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM [0005] A class of acid-labile pharmaceutical compounds that are administered as enteric-coated dosage forms are proton pump inhibiting agents. Exemplary proton pump inhibitors include, omeprazole (Prilosec®), lansoprazole (Prevacid®), **esomeprazole** (Nexium®), rabeprazole (Aciphex®), pantoprazole (Protonix®), pariprazole, tentaprazole, and leminoprazole. The drugs of this class suppress gastrointestinal acid secretion by the specific inhibition of the H.sup.+/K.sup.+-ATPase enzyme system (proton pump) at the secretory surface of the gastrointestinal parietal cell. Most proton pump inhibitors are susceptible to acid degradation and, as such, are rapidly destroyed as pH falls to an acidic level. Therefore, if the enteric-coating of these formulated products is disrupted (e.g., trituration to compound a liquid, or chewing the capsule or tablet) or the buffering agent fails to sufficiently neutralize the gastrointestinal pH, the drug will be exposed to degradation by the gastrointestinal acid in the stomach.

DETD [0029] "Anti-adherents," "glidants," or "anti-adhesion" agents prevent components of the formulation from aggregating or sticking and improve flow characteristics of a material. Such compounds include, e.g., colloidal silicon dioxide such as Cab-o-sil®; tribasic calcium phosphate, talc, corn starch, DL-leucine, sodium lauryl sulfate, magnesium stearate, calcium stearate, sodium stearate, kaolin, and micronized **amorphous** silicon dioxide (Syloid®) and the like.

DETD [0072] Proton pump inhibitors can be a substituted bicyclic aryl-imidazole, wherein the aryl group can be, e.g., a pyridine, a phenyl, or a pyrimidine group and is attached to the 4- and 5-positions of the imidazole ring. Proton pump inhibitors comprising a substituted bicyclic aryl-imidazoles include, e.g., omeprazole, hydroxyomeprazole, **esomeprazole**, lansoprazole, pantoprazole, rabeprazole, dontoprazole, habeprazole, periprazole, tenatoprazole, ransoprazole, pariprazole, leminoprazole, or a free base, free acid, salt, hydrate, ester, amide, enantiomer, isomer, tautomer, polymorph, prodrug, or derivative thereof. See, e.g., The Merck Index, Merck & Co. Rahway, N.J. (2001).

DETD [0079] Salt forms of proton pump inhibiting agents include, e.g., a sodium salt form such as **esomeprazole** sodium, omeprazole sodium, rabeprazole sodium, pantoprazole sodium; or a magnesium salt form such as **esomeprazole** magnesium or omeprazole magnesium, described in U.S. Pat. No. 5,900,424; or a calcium salt form; or a potassium salt form such as the potassium salt of **esomeprazole** , described in U.S. patent application Ser. No. 02/0198239 and U.S. Pat. No. 6,511,996. Other salts of **esomeprazole** are described in U.S. Pat. No. 4,738,974 and U.S. Pat. No. 6,369,085. Salt forms of pantoprazole and lansoprazole are discussed in U.S. Pat. Nos. 4,758,579 and 4,628,098, respectively.

CLM What is claimed is:

2. A pharmaceutical formulation according to claim 1, wherein the proton pump inhibitor is a substituted bicyclic aryl-imidazole selected from the group consisting of omeprazole, hydroxyomeprazole,

esomeprazole, tenatoprazole, lansoprazole, pantoprazole, rabeprazole, dontoprazole, habeprazole, perprazole, ransoprazole, pariprazole, leminoprazole; or a free base, free acid, salt, hydrate, ester, amide, enantiomer, isomer, tautomer, polymorph, or prodrug thereof.

4. A pharmaceutical formulation according to claim 1, wherein the proton pump inhibitor is **esomeprazole**, or a free base, free acid, salt, hydrate, ester, amide, enantiomer, isomer, tautomer, polymorph, or prodrug thereof.

30. A pharmaceutical formulation according to claim 27, wherein the proton pump inhibitor is a substituted bicyclic aryl-imidazole selected from the group consisting of omeprazole, hydroxyomeprazole, **esomeprazole**, tenatoprazole, lansoprazole, pantoprazole, rabeprazole, dontoprazole, habeprazole, perprazole, ransoprazole, pariprazole, leminoprazole; or a free base, free acid, salt, hydrate, ester, amide, enantiomer, isomer, tautomer, polymorph, or prodrug thereof.

32. A pharmaceutical formulation according to claim 27, wherein the proton pump inhibitor is **esomeprazole**, or a free base, free acid, salt, hydrate, ester, amide, enantiomer, isomer, tautomer, polymorph, or prodrug thereof.

L2 ANSWER 6 OF 42 USPATFULL on STN

ACCESSION NUMBER:	2004:315266 USPATFULL		
TITLE:	Novel formulation, omeprazole antacid complex-immediate release for rapid and sustained suppression of gastric acid		
INVENTOR(S):	Hepburn, Bonnie, Escondido, CA, UNITED STATES Goldlust, Barry, San Diego, CA, UNITED STATES		

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2004248942	A1	20041209	
APPLICATION INFO.:	US 2004-783871	A1	20040220	(10)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 2003-448627P	20030220	(60)

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FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	WILSON SONSINI GOODRICH & ROSATI, 650 PAGE MILL ROAD, PALO ALTO, CA, 943041050
NUMBER OF CLAIMS:	53
EXEMPLARY CLAIM:	1
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CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention is directed to methods, kits, combinations, and compositions for treating, preventing or reducing the risk of developing a gastrointestinal disorder or disease, or the symptoms associated with, or related to a gastrointestinal disorder or disease in a subject in need thereof. In one aspect, the present invention provides a pharmaceutical composition comprising a proton pump inhibiting agent and a buffering agent for oral administration and ingestion by a subject. Upon administration, the composition contacts the gastric fluid of the stomach and increases the gastric fluid pH of the stomach to a pH that substantially prevents or inhibits acid degradation of the proton pump inhibiting agent in the gastric fluid and allows a measurable serum

concentration of the proton pump inhibiting agent to be absorbed into the blood serum of the subject.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM [0008] Proton pump inhibitors are acid labile and therefore have been formulated as enteric-coated dosage forms to prevent acid degradation. Examples include, omeprazole (Prilosec®), lansoprazole (Prevacid®), **esomeprazole** (Nexium®), rabeprazole (Aciphex®), pantoprazole (Protonix®), pariprazole and leminoprazole. Prilosec® (omeprazole) is formulated as enteric-coated granules in gelatin capsules. Prevacid® (lansoprazole) is available as enteric-coated granules in gelatin capsules, and as enteric-coated microspheres for use as a liquid suspension. Nexium® (**esomeprazole** magnesium) is enteric-coated granules in gelatin capsules. Although these drugs are stable at alkaline pH, they are destroyed rapidly as pH falls (for example, by gastric acid). Therefore, if the enteric-coating is disrupted (for example, through trituration to compound a liquid or by chewing), the dosage forms of the prior art will be exposed to degradation by the gastric acid in the stomach.

SUMM [0017] Proton pump inhibitors include, but are not limited to, omeprazole, hydroxyomeprazole, **esomeprazole**, tenatoprazole, lansoprazole, pantoprazole, rabeprazole, dontoprazole, habeprazole, periprazole, ransoprazole, pariprazole, leminoprazole; or a free base, free acid, salt, hydrate, ester, amide, enantiomer, isomer, tautomer, polymorph, or prodrug thereof. In one embodiment, the proton pump inhibitor is omeprazole or a free base, free acid, salt, hydrate, ester, amide, enantiomer, isomer, tautomer, polymorph, or prodrug thereof. Compositions can contain between about 5 mgs to about 500 mgs of proton pump inhibitor, specifically about 10 mg, about 15 mg, about 20 mg, about 30 mg, about 40 mgs, or about 60 mgs of the proton pump inhibitor.

DETD [0077] While the present invention may be embodied in many different forms, several specific embodiments are discussed herein with the understanding that the present disclosure is to be considered only as an exemplification of the principles of the invention, and it is not intended to limit the invention to the embodiments illustrated. For example, where the present invention is illustrated herein with particular reference to omeprazole, hydroxyomeprazole, **esomeprazole**, tenatoprazole, lansoprazole, pantoprazole, rabeprazole, dontoprazole, habeprazole, periprazole, ransoprazole, pariprazole, or leminoprazole, it will be understood that any other proton pump inhibiting agent, if desired, can be substituted in whole or in part for such agents in the methods, kits, combinations, and compositions herein described.

DETD [0083] "Anti-adherents," "glidants," or "anti-adhesion" agents prevent components of the formulation from aggregating or sticking and improve flow characteristics of a material. Such compounds include, e.g., colloidal silicon dioxide such as Cab-o-sil®; tribasic calcium phosphate, talc, corn starch, DL-leucine, sodium lauryl sulfate, magnesium stearate, calcium stearate, sodium stearate, kaolin, and micronized **amorphous** silicon dioxide (Syloid®)and the like.

DETD [0141] Illustratively, a substituted benzimidazole of interest that can be used in the methods, kits, combinations, and compositions of the present invention includes, but is not limited to, omeprazole, hydroxyomeprazole, lansoprazole, pantoprazole, rabeprazole, dontoprazole, **esomeprazole** (also known as **s-omeprazole** or perprazole), tenatoprazole, habeprazole, ransoprazole, pariprazole, and leminoprazole; or a free base, free acid, salt, hydrate, ester, amide, enantiomer, isomer, tautomer, polymorph,

prodrug, or derivative of these compounds. (Based in part upon the list provided in The Merck Index, Merck & Co. Rahway, N.J. (2001)).

DETD [0142] Examples of salt forms of proton pump inhibiting agents include, for example, a sodium salt form, such as, **esomeprazole** sodium, omeprazole sodium, rabeprazole sodium, pantoprazole sodium; or a magnesium salt form, such as, **esomeprazole** magnesium or omeprazole magnesium as described in U.S. Pat. No. 5,900,424; or a calcium salt form; or a potassium salt form, such as, the potassium salt of **esomeprazole** as described in U.S. patent application No. 2002/0198239, and U.S. Pat. No. 6,511,996. Other salts of **esomeprazole** are described in U.S. Pat. No. 4,738,974 and U.S. Pat. No. 6,369,085, for example.

DETD [0203] The present invention provides pharmaceutical compositions comprising a proton pump inhibiting agent and a buffering agent for oral administration and ingestion by a subject. The composition can comprise any suitable proton pump inhibiting agent, e.g., omeprazole, hydroxyomeprazole, **esomeprazole**, lansoprazole, pantoprazole, rabeprazole, dontoprazole, **esomeprazole** (also known as **s-omeprazole** or perprazole), habeprazole, perprazole, ransoprazole, pariprazole, and leminoprazole; or a free base, free acid, a salt, hydrate, ester, amide, enantiomer, isomer, tautomer, polymorph, prodrug, or derivative of these compounds. The composition can comprise any suitable buffering agent, that, when formulated or delivered before, during and/or after the proton pump inhibiting agent, functions to substantially prevent or inhibit the acid degradation of the proton pump inhibiting agent by gastric acid sufficient to preserve the bioavailability of the proton pump inhibiting agent administered, such as, for example, sodium salts, potassium salts, magnesium salts, calcium salts, aluminum hydroxide, aluminum hydroxide/sodium bicarbonate coprecipitate, a mixture of an amino acid and a buffer, a mixture of aluminum glycinate and a buffer, a mixture of an acid salt of an amino acid and a buffer, and a mixture of an alkali salt of an amino acid and a buffer, or any other suitable buffering agent or mixture of buffering agents. In one embodiment, the present invention relates to a pharmaceutical composition comprising a proton pump inhibiting agent, a buffering agent, and optionally a parietal cell activator.

DETD [0262] It will be understood that the amount of proton pump inhibiting agent and/or buffering agent that is administered to a subject is dependent on, for example, the sex, general health, et, and/or body weight of the subject. Illustratively, where the agent is a substituted benzimidazole such as, for example, omeprazole, lansoprazole, pantoprazole, rabeprazole, **esomeprazole**, pariprazole, or leminoprazole, and the subject is, for example, a child or a small animal (for example, a dog), a relatively low amount of the agent in the dose range of about 1 mg to about 60 mg is likely to provide blood serum concentrations consistent with therapeutic effectiveness. Where the subject is an adult human or a large animal (for example, a horse), achievement of such blood serum concentrations of the agent are likely to require dose units containing a relatively greater amount of the agent, for example, a 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 g, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, 105 mg, 110 mg, 115 mg, or 120 mg dose for an adult human, or a 150 mg, 200 mg, 400 mg, 800 mg, or 1000 mg dose for an adult horse.

DETD [0295] Prilosec® capsules containing enteric-coated omeprazole granules (40 mg) and Nexium®D capsules containing enteric-coated **esomeprazole** granules (40 mg) are marketed by AstraZenecae.

DETD [0310] OSB-IR PWD F/S: **Omeprazole** sodium bicarbonate, immediate-release, powder for suspension

DETD [0338] Period 4: One Nexium.TM. tablet (40 mg **esomeprazole**) administered 30 minutes prior to ingestion of a standard breakfast

DETD [0351] Period 4: A single 40 mg oral dose of one Nexium.TM. capsule (**esomeprazole**, US formulation) administered 90 minutes after a

standardized breakfast.

DETD [0357] Pharmacokinetic evaluations include plasma omeprazole and **esomeprazole** concentration over time; and plasma omeprazole and **esomeprazole** C.sub.max, T.sub.max, k.sub.el, T.sub.1/2, AUC.sub.(0-t), and AUC.sub.(0-inf). Pharmacodynamic evaluation can include onset time of gastric pH increase, gastric pH over time, and % time pH>4.

DETD [0381] The pharmacokinetic profiles of omeprazole powder plus chewable antacid tablets, omeprazole powder alone, Prilosec® capsules (omeprazole), and Nexium® capsules (**esomeprazole** magnesium) in the context of different dosing regimens relative to the ingestion of meals were performed as described in the SAN-15-C01C trial protocol. These results from trial SAN-15-C01C, summarized in Table 3.A).

TABLE 3.A

Pharmacokinetics of Omeprazole Powder (40 mg) Administered With or Without Antacid (Pre-meal)

	Number of Subjects	C.sub.max ng/mL (Median)	AUC.sub.(0-t)ng + hr/mL (Median)
Control	10	--	--
Omeprazole Powder Administered 1 hour Pre-meal	10	186.4	225
Omeprazole Powder Plus 30 mEq Antacid Administered 1 hour Pre-meal	10	911.5	965.7

CLM What is claimed is:

16. The pharmaceutical composition of claim 1, wherein the proton pump inhibitor is selected from the group consisting of omeprazole, hydroxyomeprazole, **esomeprazole**, tenatoprazole, lansoprazole, pantoprazole, rabeprazole, dontoprazole, habeprazole, perprazole, ransoprazole, pariprazole, leminoprazole; or a free base, free acid, salt, hydrate, ester, amide, enantiomer, isomer, tautomer, polymorph, derivative, or prodrug thereof.

19. The pharmaceutical composition of claim 1, wherein the proton pump inhibitor comprises **esomeprazole**, or a free base, free acid, salt, hydrate, ester, amide, enantiomer, isomer, tautomer, polymorph, derivative, or prodrug thereof.

L2 ANSWER 7 OF 42 USPATFULL on STN

ACCESSION NUMBER: 2004:307966 USPATFULL

TITLE: Crystalline **esomeprazole** compounds and process for the preparation thereof

INVENTOR(S): Reddy, Manne Satyanarayana, Hyderabad, INDIA
Kumar, Muppa Kishore, Hyderabad, INDIA
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PATENT ASSIGNEE(S): DR. REDDY'S LABORATORIES LIMITED (non-U.S. corporation)
DR. REDDY'S LABORATORIES, INC. (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2004242642	A1	20041202	
APPLICATION INFO.:	US 2003-716200	A1	20031118	(10)

	NUMBER	DATE
PRIORITY INFORMATION:	IN 2002-8522002	20021118

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LEGAL REPRESENTATIVE: Ladas & Parry, 26 West 61 Street, New York, NY, 10023
NUMBER OF CLAIMS: 35
EXEMPLARY CLAIM: 1
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CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to crystalline form II of **esomeprazole** trihydrate and methods of its preparation and use. Preferably, the crystalline form II of **esomeprazole** trihydrate has an X-ray powder diffraction pattern that includes five or more peaks with 2 theta angles of 4.82±0.09, 5.55±0.09, 7.41±0.09, 8.60±09, 12.10±0.09, 14.16±0.09, 18.47±0.09, and 21.08±0.09.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Crystalline **esomeprazole** compounds and process for the preparation thereof

AB The present invention relates to crystalline form II of **esomeprazole** trihydrate and methods of its preparation and use. Preferably, the crystalline form II of **esomeprazole** trihydrate has an X-ray powder diffraction pattern that includes five or more peaks with 2 theta angles of 4.82±0.09, 5.55±0.09, 7.41±0.09, 8.60±09, 12.10±0.09, 14.16±0.09, 18.47±0.09, and 21.08±0.09.

SUMM [0002] The present invention relates to a crystalline form of hydrated **esomeprazole** salt and in particular to **esomeprazole** magnesium trihydrate salt, chemically known as (S)(-)5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulphinyl]-1H-benzimidazole trihydrate.

SUMM [0003] **Esomeprazole** is the (S)(-) enantiomer of omeprazole, a sulfoxide which has an asymmetric center at the sulfur atom and exists as optical isomers (enantiomers). **Esomeprazole** ((S)(-)5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulphinyl]-1H-benzimidazole) is the S(-)enantiomer of the drug omeprazole. Known forms of **esomeprazole**, and its salts, hydrates, and polymorphs, are gastric acid secretion inhibitors.

SUMM [0004] Omeprazole, and its therapeutically acceptable alkaline salts are disclosed in EP 000 5129 and EP 124,495 respectively, while DE 4035455 discloses separation of the enantiomers of omeprazole using diastereomeric ether. WO 00/44744 discloses the potassium salt of **esomeprazole**. U.S. Pat. No. 6,162,816 discloses crystalline form A and less crystalline form B of neutral **esomeprazole**, prepared by a recrystallization from ethyl acetate, methylene chloride or toluene.

SUMM [0005] U.S. Pat. No. 6,369,085, which is incorporated herein by reference in its entirety, discloses **esomeprazole** magnesium trihydrate prepared from the corresponding potassium salt, precipitated with acetone, and treated with water. The crystalline form of the '085 patent will be designated herein as crystalline form I.

SUMM [0006] A number of drugs have been found to exhibit desirable dissolution characteristics and, in some cases, desirable bioavailability patterns when used in a specific solid form, e.g., as an **amorphous** or crystalline solid. Therefore, there is a continuing

need for new solid forms of **esomeprazole** and methods of their preparation.

SUMM [0007] In one aspect, the invention provides a compound which is a crystalline form II of **esomeprazole** magnesium trihydrate. Preferably, the compound of this aspect of the invention has an X-ray powder diffraction pattern expressed the terms of 2 theta angles and obtained with a diffractometer equipped with a copper K X-radiation source, wherein said X-ray powder diffraction pattern includes five or more peaks selected from the group consisting of peaks with 2 theta angles of 4.82±0.09, 5.55±0.09, 7.41±0.09, 8.60±09, 12.10±0.09, 14.16±0.09, 18.47±0.09, and 21.08±0.09.

SUMM [0008] In another aspect, the invention provides a composition comprising solid **esomeprazole** magnesium, wherein at least 75% of said **esomeprazole** magnesium is a crystalline form II of **esomeprazole** magnesium tribydrate. Preferably, the composition is substantially free of other forms of **esomeprazole** and is a solid powder of bulk **esomeprazole** magnesium for use as an active pharmaceutical ingredient.

SUMM [0009] In yet another aspect, the invention provides a process for making a trihydrate of **esomeprazole** magnesium in the form of a crystalline solid that includes:

SUMM [0010] a) providing **esomeprazole** magnesium as a solution in a ketone-containing solvent;

SUMM [0012] c) isolating the separated solid mass, which is the trihydrate of **esomeprazole** magnesium in the form of a crystalline solid. The preferred alcohol-containing solvent is methanol, ethanol, propanol, and butanol; methanol is more preferred. The preferred ketone-containing solvent is a mixture of acetone and water. In a more preferred embodiment of this aspect, the invention provides a process for making a trihydrate of **esomeprazole** magnesium in the form of a crystalline solid that includes:

SUMM [0013] a) providing **esomeprazole** magnesium in methanol;

SUMM [0014] b) contacting the **esomeprazole** magnesium in methanol with water so that a solid mass separates;

SUMM [0020] h) drying the isolated residual mass, which is the trihydrate of **esomeprazole** magnesium in the form of a crystalline solid.

SUMM [0021] The invention also provides a pharmaceutical composition containing the crystalline form II of **esomeprazole** magnesium trihydrate, and methods of administration related thereto.

DRWD [0022] FIG. 1 shows an example of x-ray powder diffraction pattern (XRD) for crystalline form II of **esomeprazole** magnesium trihydrate.

DETD [0034] In one aspect, the invention provides a new crystalline form of **esomeprazole** magnesium trihydrate salt herein designated a crystalline form II, which is believed to have a unique X-ray diffractogram. **Esomeprazole** ((S)(-)5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulphinyl]-1 H-benzimidazole; the S(-)enantiomer of omeprazole), as well as its salts, is an active gastric acid secretion inhibitor. Preferably, the crystalline Form II of **esomeprazole** magnesium is substantially free of R-omeprazole magnesium salt. It can be synthesized with good reproducibility, favoring large-scale production. It is also obtainable as a free flowing and non-solvated crystalline solid, a form useful in pharmaceutical

formulations.

DETD [0036] For crystalline compounds, XRD (x-ray powder diffraction) is a useful characterization tool. Each XRD is unique for the particular crystalline form. Each crystalline form exhibits a diffraction pattern with a unique set of diffraction peaks that can be expressed in 2 theta angles, d-spacing values and relative peak intensities. 2 theta diffraction angles and corresponding d-spacing values account for positions of various peaks in the XRD pattern, and d-spacing values may calculated with observed 2 theta angles and copper K(α1) wavelength by well known methods using the Bragg equation. FIG. 1 shows the X-ray diffractogram of one batch of solid crystalline form II of **esomeprazole** magnesium trihydrate obtained by the inventors (the process of making the solid crystalline form II of **esomeprazole** magnesium trihydrate is described in greater details below). The x-ray powder diffractogram was measured on a Bruker Axs, D8 Advance X-ray Powder diffractometer with Cu K alpha-1 radiation source. The XRD data for the crystalline form II of **esomeprazole** magnesium trihydrate as obtained by the inventors are as follows:

2-theta value	Relative Intensity (%)
4.824	100.0
18.471	81.7
5.552	43
14.16	28.1
12.104	25.3
8.608	22.3
21.089	21.5
7.411	18.8

DETD [0037] The crystalline form II of **esomeprazole** magnesium trihydrate may be identified by x-ray diffraction. One method of identifying particular crystalline forms is to compare their XRD patterns. If the comparison shows that the two patterns are similar to each other within a technically reasonable range as a skilled person would understand, then the two compared crystalline forms are substantially the same. For example, one skilled in the art can overlay an XRD pattern of an unidentified crystalline form obtained using the methods described herein, over the XRD in FIG. 1 and readily determine whether the XRD pattern of the unidentified form is substantially the same as the XRD pattern in FIG. 1. Of course, slight variations in observed 2 theta angles or d-spacing values are expected based on the specific diffractometer employed and the sample preparation technique. More variation is expected for the relative peak intensities. Therefore identification of the exact crystal form of a compound should be based primarily on observed 2 theta angles with lesser importance attributed to relative peak intensities. For these reasons, some margin of error is present in each of the 2 theta angle assignments and d-spacings reported herein. The margin of error assigned herein for the 2 theta angles is approximately ±0.09 for each of the peak assignments. For this reason, the crystalline form II of **esomeprazole** magnesium trihydrate is believed to have an X-ray powder diffraction pattern that includes five or more peaks selected from the group consisting of peaks with 2 theta angles of 4.82±0.09, 5.55±0.09, 7.41±0.09, 8.60±09, 12.10±0.09, 14.16±0.09, 18.47±0.09, and 21.08±0.09.

DETD [0039] In another aspect, the invention provides a composition including **esomeprazole** magnesium as a solid, in which at least 80%, preferably 90%, more preferably 95%, and most preferably 99% by weight of the crystalline form II of **esomeprazole** magnesium trihydrate. The remainder of the **esomeprazole** magnesium in the

composition, e.g., 20%, preferably 10%, more preferably 5%, and most preferably 1% or less of the total weight of **esomeprazole** magnesium, may be **amorphous** or one or more other crystalline forms of **esomeprazole** magnesium. In one embodiment of this composition, the solid **esomeprazole** magnesium is substantially free from **amorphous** forms of **esomeprazole** magnesium.
In yet another embodiment, in addition to the crystalline form II of **esomeprazole** magnesium trihydrate, the composition includes at least a small amount of an **amorphous** form of **esomeprazole** magnesium. In a non-limiting example, the composition includes 95% of the crystalline form II of **esomeprazole** magnesium trihydrate and at least 1% of an **amorphous** form of **esomeprazole** magnesium. In another non-limiting example, the composition includes at least 80% of the trihydrate of **esomeprazole** magnesium in the form of an crystalline solid and at least 5% of the **amorphous** form of **esomeprazole** magnesium. All compositions, in 0.1% increments, which include at least 80% of the crystalline form II of **esomeprazole** magnesium trihydrate and at least 1% of the **amorphous** form of **esomeprazole** magnesium, are contemplated. All percentages are based upon the total amount of the solid **esomeprazole** magnesium in the composition. The preferred form of the composition of this aspect of the invention is a solid powder of bulk **esomeprazole** magnesium for use as an active pharmaceutical ingredient. This powder composition has a moisture content, which is preferably from about 7% to about 8%. Moisture content may be measured by any accepted technology, for example by using Karl Fischer reagent (KF) and an appropriate instrument (goniometer) such as a Mettler DL-35, a Scintag PAD V, a Brukker D5000, or by thermogravimetric analysis using moisture analysis instruments such as the Mettler DSC20, TG50, and TC10A.

DETD [0040] To determine the relative amounts of **amorphous** and crystalline components in the composition of this aspect of the invention, one suitable analytical methodology is X-ray powder diffraction (XRD). XRD methodology is capable of providing both qualitative and quantitative information about compounds present in a solid sample. XRD is adaptable to quantitative applications because the intensities of the diffraction peaks of a given compound in a mixture are proportional to the fraction of the material in the mixture. By measuring the intensity of the diffraction lines and comparing them with standards, it is possible to make a quantitative analysis of crystalline mixtures.

DETD [0041] As explained above, **amorphous** solids have no characteristic peaks. In contrast, each crystalline solid is arranged in a set of planes separated by interplanar space d, and exhibits a diffraction pattern with a unique set of peaks generated when x-rays strike a plane at angle theta and are diffracted at the same angle, thus the 2 theta angle is determined by the spacing between a particular set of planes. The identification of a crystalline solid is based upon peaks in the XRD pattern being tabulated in terms the diffraction angle 2 theta (or d-spacing) and their relative intensities. Identification of a crystal form of a compound should be based primarily on observed 2 theta angles with lesser importance being attributed to relative peak intensities. Different quantitative techniques are available. For example, two methods may be used to analyze XRD quantitatively: the Internal Standard Method and the External Standard Method. The Internal Standard Method is the preferred procedure for analyzing powdered systems. This method measures a known quantity of a reference powder which is added to an unknown powder. The mass absorption coefficient of the mixture need not be known in advance. Any number of constituents in the mixture may be quantified independently, including the **amorphous** (non-crystalline) components. The External Standard

Method is used to analyze solid systems when the mass absorption co-efficient is known. It allows the quantification of one or more components in a system, which may contain an **amorphous** fraction. The percent composition of a crystalline compound can be determined in an unknown composition. The XRD patterns of an unknown composition can be compared to a known standard containing pure crystalline compound to identify the percent ratio of the crystalline form of the compound. This is done by comparing the relative intensities of the peaks from the diffraction pattern of the unknown composition with a calibration curve based on the XRD pattern for the strongest peak derived from the XRD pattern of a pure crystalline sample of the compound. The peak intensities are reported as intensities relative to the peak intensity of the strongest peak ("the 100% peak"). The calibration curve may be created in a manner known to those of skill in the art. For example, five or more artificial mixtures of **amorphous** and crystalline forms of crystalline compound in different amounts, may be prepared. As an example, such mixtures may contain, 2%, 5%, 7%, 8%, and 10% of crystalline compound, with the remainder being the **amorphous** form of the salt. Then, XRD patterns are obtained for each artificial mixture using standard XRD techniques. Slight variations in peak positions, if any, may be accounted for by adjusting the location of the peak to be measured. The intensities of the 100% peak(s) for each of the artificial mixtures are then plotted against the known weight percentages of the crystalline form. The resulting plot is a calibration curve that allows determination of the amount of crystalline compound in an unknown sample. For the unknown mixture of crystalline and **amorphous** compounds, the intensities of the 100% peak(s) in the mixture, relative to an intensity of this peak in a calibration mixture, may be used to determine the percentage of the crystalline form in the composition, with the remainder determined to be the **amorphous** material.

DETD [0042] In order to determine the relative amount of **amorphous** to crystalline solid in the compositions of this invention, XRD information may be used to create the calibration curve(s) described above. For use in this comparative analysis, XRD patterns of crystalline forms of **esomeprazole** are obtainable by known methods of measurement. For example, the XRD data for crystalline Form I **esomeprazole** magnesium trihydrate is disclosed in U.S. Pat. No. 6,369,085, which is incorporated by reference for this purpose.

DETD [0043] In another aspect, the invention provides a process for making the crystalline form II **esomeprazole** magnesium trihydrate by a) providing **esomeprazole** magnesium as a solution in a ketone-containing solvent; b) cooling the solution so that a solid mass separates; and c) isolating the separated solid mass, which is the trihydrate of **esomeprazole** magnesium in the form of a crystalline solid; particularly, the crystalline form II of **esomeprazole** magnesium trihydrate. The starting materials and reagents used in this process are commercially available and/or may be readily synthesized by a skilled person, unless otherwise indicated. **Esomeprazole** base may be made as known in the art. See in addition U.S. Pat. Nos. 6,162,816 and 5,693,818, which are incorporated herein by reference. Any conventional aqueous or organic solvent that would not hinder or would contribute to the reactions by which the process of the invention proceeds may be included in the ketone-containing solvent. Non-limiting examples of suitable ketones include acetone, ethyl methyl ketone, methyl isobutyl ketone, and diethyl ketone. The preferred ketone-containing solvent is a mixture of acetone and water. Examples of organic solvents include chlorinated alkanes, such as chloroform, dichloromethane, dichloroethane, and carbon tetrachloride; ester solvents such as lower alkyl esters of organic acids, such as methyl, ethyl, propyl isopropyl, butyl, isobutyl, and tert-butyl acetate; and nitriles, such as acetonitrile. Preferably, the

alcohol component of the alcohol-containing solvent is preferably methanol, ethanol, propanol, or butanol, more preferably ethanol, n-propanol, tert-butanol, n-butanol, and most preferably methanol. The alcohol-containing solvent may be a pure alcohol (for example, methanol) or may be a mixture of alcohol with other solvent(s), for example with water, with a ketone solvent such as acetone, or with both. Preferably the alcohol-containing solvent includes methanol.

DETD [0044] Certain operational steps are well known in the art and, unless otherwise indicated, any known method for performing these functions may be used in the processes of this invention. For example, solvents may be removed by distillation in atmosphere or under vacuum. Drying may be accomplished by evaporation, spray drying, drying under vacuum, and freeze-drying. Stirring means any method for blending or mixing a reaction mixture. Reagents and/or reaction mixtures may be combined by adding one to the other, for example, water may be poured into a reaction mixture. **Esomeprazole** magnesium may be provided, for example, by suspending magnesium metal in an alcohol-containing solvent in the presence of a haloalkane and adding **esomeprazole** base (which may itself be dissolved in an alcohol-containing solvent). Preferred haloalkanes are dichloromethane, dichloromethane (in particular 1,2-dichloroethane) and trichloromethane (chloroform); most preferably, dichloromethane. The process then continues by contacting with water. Contacting with water may be accomplished by pouring water into the **esomeprazole** magnesium solution, or by pouring the **esomeprazole** magnesium solution into water, or by other conventional methods. The preferred amounts of alcohol-containing solvent and of water in milliliters (ml) may be determined relative to the amount of the starting **esomeprazole** magnesium (i.e., the **esomeprazole** magnesium in the alcohol-containing solvent provided in the first step of the process) in grams (g). The amount of alcohol-containing solvent is preferably about 5 ml to about 10 ml per 1 gram of the starting **esomeprazole** magnesium, preferably about 6 to about 7 ml. The amount of water is preferably about 5 ml to about 25 ml per 1 gram of the starting **esomeprazole** magnesium, preferably, about 18 ml.

DETD [0045] The resulting solid mass of **amorphous esomeprazole** magnesium may be then recrystallized from the ketone-containing solvent (e.g., acetone/water mixture) to obtain the crystalline form II **esomeprazole** magnesium trihydrate. The solid mass is isolated, washed by a suitable solvent, such as water or a ketone solvent such as acetone, preferably once with water and once with acetone. However the solid mass may be washed sequentially in these solvents in any combination, for example twice with water and once with the ketone solvent, or the reverse, and so on. It is also helpful to dissolve the isolated solid mass (preferably after filtration, or after filtration and washing) in an alcohol such as methanol. At this stage the solution formed by dissolving the solid mass in the alcohol may be filtered to separate the excess magnesium, which may then be removed by conventional methods. The solution formed by dissolving the isolated solid mass in alcohol is treated to obtain solid material again in the form of an isolated mass. Solvent may be removed from the solution to accomplish this, using conventional methods. The isolated residual mass is preferably re-precipitated, for example from an ester solvent such as ethyl acetate.

DETD [0046] The specific non-limiting example of this process includes a) disoolving magnesium metal in the alcohol-containing solvent; b) cooling the mass to 5-10 degrees C.; c) adding **esomeprazole** base as a solution an alcohol-containing solvent (same or different); d) slowly decomposing the reaction mixture by adding water and storring until a mass separates; e) filtering the isolated solid; f) suspending the wet solid in acetone and storring for 1-2 hours at 5-10 degrees C.; g) filtering the solid; h) dissolving the solid (or external

esomeprazole amorphous) in an alcohol-containing solvent (same or different); k) removing the solvent; 1) dissolving the residue in a ketone-containing solvent; m) cooling the mass to from -10 to +10 degrees C. until a mass separates; n) filtering the solid, which is the crystalline form II of **esomeprazole** magnesium trihydrate; and o0 drying the obtained crystalline form II of **esomeprazole** magnesium trihydrate at 50-100 degrees C., preferably at 50-70 degrees C.

DETD [0047] In another aspect, the invention provides pharmaceutical compositions which include the crystalline form II **esomeprazole** magnesium trihydrate. Pharmaceutical compositions generally contain, in addition to the active compound or compounds, one or more carriers (also called excipients) which ordinarily lack pharmaceutical activity per se, but have various useful properties which can, for example, enhance the stability, sterility, bioavailability, and ease of formulation of a pharmaceutical composition. These carriers are pharmaceutically acceptable, meaning that they are not harmful to humans or animals when taken appropriately and are compatible with the other ingredients in a given formulation. The carrier may be solid, semi-solid, or liquid, and may be formulated with the compound in bulk, but ultimately in the form of a unit-dose formulation (i.e., a physically discrete unit containing a specific amount of active ingredient) such as a tablet or capsule.

DETD [0049] The amount of active ingredient included in a unit dosage form depends on the type of formulation in which the active ingredient is presented. A pharmaceutical composition will generally contain about 0.1% by weight to about 99% by weight of the crystalline form II of **esomeprazole** magnesium trihydrate, preferably about 1% by weight to 50% by weight for oral administration and about 0.2% by weight to about 20% by weight for parenteral administration.

DETD [0055] Also part of this invention are methods of treatment using one or more of the compounds of this invention and the pharmaceutical compositions of this invention. In particular, the crystalline form II of **esomeprazole** magnesium trihydrate may be administered to a subject in an amount effective to reduce secretion of gastric acid by that subject. Although it is possible to use compounds and compositions of this invention to prevent secretion of gastric acid by establishing a dosage level effective to do so, such treatment would only be applicable in special cases, since to alleviate or eliminate most of the conditions discussed above which are treated with the compounds of this invention, gastric acid secretion should not be eliminated altogether, but only reduced in amount or duration. In general, the treatment may be determined to alleviate, to eliminate, or to prevent a given condition based on factors determinable by a skilled physician as discussed below in the context of determining an effective amount for dosage. Further, the compounds of this invention may be administered to a subject for treating a disorder caused by gastric acid secretion by administering to a subject an amount effective to reduce gastric acid secretion by said subject.

DETD Preparation of Novel Crystalline Form II of **Esomeprazole** Magnesium Trihydrate Salt from Crude **Esomeprazole**

DETD [0060] Magnesium metal (2.08 grams) was suspended in a mixture of methanol (150.00 ml) and dichloromethane (5.0 ml) and cooled to a temperature of 5-10° C. Then, to the resulting reaction mixture crude **esomeprazole** (50.0 grams)] dissolved in methanol (150.0 ml) was added. The resulting reaction mixture was slowly decomposed by adding water (900 ml) and stirred until a solid results. The resulting solid mass was filtered and washed with water (300 ml). The wet solid was suspended in acetone (200 ml) and stirred at a temperature of 0-5° C. until the solid separated. The separated solid was filtered and washed with acetone (50 ml). Further the wet solid was dissolved in methanol (300 ml) and filtered. Then by expelling the resulting filtrate white solid was isolated. The isolated white solid

was recrystallised from a mixture of water (175 ml) and acetone (175 ml). The crystallized solid was dried at a temperature of 60-65° C. to afford the title compound. [Weight: 8.5 grams).

DETD Preparation of Crystalline Form II of **Esomeprazole** Magnesium Trihydrate Salt from **Amorphous** Form of **Esomeprazole**

DETD [0061] The **amorphous** form of **esomeprazole** magnesium salt (25 grams) was dissolved in methanol (100.00 ml). The resulting reaction solution was filtered through a high-flow bed and the bed washed with methanol (50 ml). Then the solvent was distilled off completely from the reaction solution, water (50 ml) added to the resulting residue and the reaction mixture stirred until the solid resulted. The resulting solid mass was suspended in mixture of water (300 ml) and acetone (300 ml), and stirred at a temperature of 0-5° C. until solid separated. THe separated solid was filtered and washed with mixture of water (50 ml) and acetone (50 ml). Further the wet solid was suck dried at a temperature of 60-70° C. to afford the title compound. [Weight: 14.8 grams). The exemplified compounds have a moisture content in the range of 7.0 to 8.0% measured on a Mettler DL-35 using Karl-Fischer reagent by the Karl Fischer method. This moisture content indicates a trihydrate salt.

CLM What is claimed is:

1. A compound which is a crystalline form II of **esomeprazole** magnesium trihydrate.

7. A composition comprising **esomeprazole** magnesium, wherein at least 75% of said **esomeprazole** magnesium is a crystalline form II of **esomeprazole** magnesium trihydrate.

8. The composition of claim 7, which comprises at least 90% of said **esomeprazole** magnesium is the crystalline form II of **esomeprazole** magnesium.

9. The composition of claim 8, wherein at least 95% of said **esomeprazole** magnesium is the crystalline form II of **esomeprazole** magnesium.

10. The composition of claim 7, which is substantially free of other forms of **esomeprazole** magnesium.

11. The composition of claim 7, which is a solid powder of bulk **esomeprazole** magnesium for use as an active pharmaceutical ingredient.

14. The composition of claim 7, wherein 20% or less by weight of the solid **esomeprazole** magnesium is in **amorphous** form.

15. The composition of claim 14, wherein 10% or less by weight of the solid **esomeprazole** magnesium is in **amorphous** form.

16. The composition of claim 14, wherein 5% or less by weight of the solid **esomeprazole** magnesium is in **amorphous** form.

17. The composition of claim 14, wherein 1% or less by weight of the solid **esomeprazole** magnesium is in **amorphous** form.

18. The composition of claim 14, wherein said solid **esomeprazole** magnesium is substantially free of the **amorphous** form of **esomeprazole** magnesium.

19. A process for making a trihydrate of **esomeprazole** magnesium in the form of a crystalline solid, said process comprising: a) providing **esomeprazole** magnesium as a solution in a

ketone-containing solvent; b) cooling said solution so that a solid mass separates; and c) isolating said separated solid mass, which is the trihydrate of **esomeprazole** magnesium in the form of a crystalline solid.

20. The process of claim 19, wherein said solution is provided by dissolving **amorphous esomeprazole** magnesium in said ketone-containing solvent.

21. The process of claim 20, wherein said **amorphous esomeprazole** magnesium is obtained by suspending magnesium metal in said alcohol-containing solvent in the presence of a haloalkane and adding **esomeprazole** base thereto.

28. The process of claim 27, wherein the amount of alcohol-containing solvent is about 5 ml to about 10 ml per 1 gram of the starting **esomeprazole** magnesium.

29. The process of claim 27, wherein the amount of water is about 5 ml to about 25 ml per 1 gram of the starting **esomeprazole** magnesium.

31. A process for making a trihydrate of **esomeprazole** magnesium in the form of a crystalline solid, said process comprising: a) providing **esomeprazole** magnesium in methanol; b) contacting said **esomeprazole** magnesium in methanol with water so that a solid mass separates; c) isolating said solid mass by filtration; d) washing said solid mass; e) dissolving said solid mass in methanol and filtering the solution so formed to separate excess magnesium solids; f) removing solvent from the solution to obtain isolated residual mass; g) re-precipitating said isolated residual mass from a mixture of acetone and water, and h) drying said isolated residual mass, which is the trihydrate of **esomeprazole** magnesium in the form of a crystalline solid.

32. The process of claim 31, wherein the **esomeprazole** magnesium is provided by suspending magnesium metal in methanol in the presence of dichloromethane and adding **esomeprazole** base.

34. A pharmaceutical composition comprising a crystalline form II of **esomeprazole** magnesium trihydrate and a pharmaceutically acceptable carrier.

35. A method for reducing gastric acid secretion in a subject which comprises administering to the subject an amount of a crystalline form II of **esomeprazole** magnesium trihydrate effective to reduce gastric acid secretion by said subject.

36. A method for reducing gastric acid secretion in a subject which comprises administering to the subject an amount of a crystalline form II of **esomeprazole** magnesium trihydrate effective to reduce gastric acid secretion by said subject.

L2 ANSWER 8 OF 42 USPATFULL on STN
ACCESSION NUMBER: 2004:300034 USPATFULL
TITLE: **Amorphous** form of **esomeprazole** salts
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LEGAL REPRESENTATIVE: RANBAXY INC., 600 COLLEGE ROAD EAST, SUITE 2100, PRINCETON, NJ, 08540
NUMBER OF CLAIMS: 38
EXEMPLARY CLAIM: 1
LINE COUNT: 374
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention relates to an **amorphous** form of the salts of the (-) enantiomer or (S)-enantiomer of omeprazole, i.e., **esomeprazole**. The invention also relates to processes for preparing **amorphous esomeprazole** salts and pharmaceutical compositions that include the **amorphous esomeprazole** salts.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI **Amorphous** form of **esomeprazole** salts

AB The invention relates to an **amorphous** form of the salts of the (-) enantiomer or (S)-enantiomer of omeprazole, i.e., **esomeprazole**. The invention also relates to processes for preparing **amorphous esomeprazole** salts and pharmaceutical compositions that include the **amorphous esomeprazole** salts.

SUMM [0001] The field of the invention relates to an **amorphous** form of the salts of the (-) enantiomer or (S)-enantiomer of omeprazole, i.e., **esomeprazole**. The invention also relates to processes for preparing **amorphous esomeprazole** salts and pharmaceutical compositions that include the **amorphous esomeprazole** salts.

SUMM [0003] Omeprazole is a racemic mixture of its two single enantiomers, the (R)- and (S)-enantiomer of omeprazole. These enantiomers are commonly referred to as (R)-omeprazole and (**S**)-**omeprazole**, respectively. The enantiomer, (**S**)-**omeprazole**, is commonly referred to as **esomeprazole**.

SUMM [0006] **Esomeprazole**, like many other similar benzimidazole compounds, is not stable in its free form and is susceptible to degradation in acid and neutral media. It has been found that alkali metal or alkaline earth metal salts of **esomeprazole** are more stable during storage than the corresponding neutral form.

SUMM [0007] U.S. Pat. No. 5,714,505 describes alkaline salts of the (-) enantiomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridiniyl)methyl]sulfinyl]-1H-benzimidazoles (i.e., **esomeprazole**) including the magnesium salt, which are used for inhibiting gastric acid secretion. **Esomeprazole** magnesium is prepared according to Examples 5, 6, and 7 of the '505 patent in optically pure crystalline form by precipitation/crystallization.

SUMM [0008] U.S. Pat. No. 6,124,464 discloses another process for preparing crystalline **esomeprazole** magnesium. U.S. Pat. No. 6,369,085 discloses three different types of crystalline **esomeprazole**

magnesium viz. dihydrate form A, dihydrate form B and the trihydrate form. However, the inventors are not aware of any disclosure of an **amorphous** form of **esomeprazole** salts, including **amorphous esomeprazole** magnesium, in the prior art. It is known that different morphs of biologically active compounds may have different absorption profile in vivo and consequently different pharmacokinetic profile.

SUMM [0009] In one general aspect there is provided an **amorphous** form of a salt of **esomeprazole.**

SUMM [0010] Embodiments of the **amorphous** form of the salt of **esomeprazole** may include one or more of the following features. For example, the cation may be selected from the group that includes Na, Mg, Li, K, Ca, and N(R).sub.4, where R is hydrogen or an alkyl with 1-4 carbon atoms.

SUMM [0011] The **amorphous** form of the salt of **esomeprazole** may have the X-ray diffraction pattern of FIG. 1 and the IR spectra of FIG. 2.

SUMM [0012] In another general aspect there is provided a pharmaceutical composition that includes a therapeutically effective amount of an **amorphous** form of a salt of **esomeprazole**; and one or more pharmaceutically acceptable carriers, excipients or diluents.

SUMM [0014] The **amorphous** form of the salt of **esomeprazole** may have the X-ray diffraction pattern of FIG. 1 and the IR spectra of FIG. 2.

SUMM [0015] In another general aspect there is provided a process for the preparation of a salt of the **amorphous** form of **esomeprazole.** The process includes preparing a solution of a salt of **esomeprazole** in one or more solvents; and recovering the salt of **esomeprazole** in the **amorphous** form from the solution thereof by the removal of the solvent.

SUMM [0019] The salt of **esomeprazole** in an **amorphous** form may be recovered from the solution by spray drying. Alternatively, the salt of **esomeprazole** in an **amorphous** form may be recovered from the solution by freeze-drying. The process may include further forming of the product so obtained into a finished dosage form.

SUMM [0022] The process may produce the **amorphous** form of the salt of **esomeprazole** having the X-ray diffraction pattern of FIG. 1 and the IR spectra of FIG. 2.

DRWD [0024] FIG. 1 is an x-ray powder diffraction pattern of **amorphous esomeprazole.**

DRWD [0025] FIG. 2 is an infra-red spectra in KBr of **amorphous esomeprazole** magnesium prepared as described herein.

DETD [0026] The mentors have found a new form of **esomeprazole** salts, the **amorphous** form and, in particular, the **amorphous esomeprazole** magnesium salt. The new form is characterized by its X-ray powder diffraction pattern and IR spectra as shown in FIGS. 1 and 2, respectively. The inventors also have developed a process for the preparation of the **amorphous** form of **esomeprazole** salts, including the **esomeprazole** magnesium salt, by recovering the **amorphous esomeprazole** salt from a solution thereof in a suitable solvent by spray drying. The resulting **amorphous** form of salts of **esomeprazole** include, for example, Na, Mg, Li, K, Ca, and

N(R).sub.4, where R is hydrogen or an alkyl group with 1-4 carbon atoms. The inventors also have developed pharmaceutical compositions that contain the **amorphous** form of the **esomeprazole** salts, including the **esomeprazole** magnesium salt, in admixture with one or more solid or liquid pharmaceutical diluents, carriers, and/or excipients. These pharmaceutical compositions may be used for the treatment of gastric acid-related diseases by inhibition of gastric acid secretion.

DETD [0027] In general, the solution of **esomeprazole** salt may be obtained by dissolving a crystalline **esomeprazole** salt in a suitable solvent. Alternatively, such a solution may be obtained directly from a reaction in which **esomeprazole** salt is formed. The solvent may be removed from the solution by a technique which includes, for example, distillation, distillation under vacuum, evaporation, spray drying, and freeze drying.

DETD [0028] In one aspect, a salt of **esomeprazole** in **amorphous** form is recovered from the solution using a spray drying technique. A Mini-Spray Dryer (Model: Buchi 190, Switzerland) can be used. The Buchi 190 Mini-Spray Dryer operates on the principle of nozzle spraying in a parallel flow, i.e., the sprayed product and the drying gas flow in the same direction. The drying gas can be air or inert gases such as nitrogen, argon and carbon dioxide.

DETD [0029] In another aspect, a salt of **esomeprazole** in **amorphous** form can be recovered from the solution using a freeze drying technique. A freeze dryer (Model:Virtis Genesis SQ Freeze Dryer) can be used in this technique. The Virtis Genesis SQ Freeze Dryer operates on the principle of lyophilization, i.e., a process of stabilizing initially wet materials (aqueous solution or suspensions) by freezing them, then subliming the ice while simultaneously desorbing some of the bound moisture (primary drying). Following removal of the ice, desorption may be continued (secondary drying). This process may be carried out under vacuum.

DETD [0030] The term "suitable solvent" includes any solvent or solvent mixture in which **esomeprazole** salt, including **esomeprazole** magnesium, is soluble, including, for example, nitriles, cyclic ethers, lower alkanol, ketones, esters, chlorinated solvents, acetonitrile and mixtures thereof. Examples of alcohols include methanol, ethanol, isopropanol, and the like. Examples of halogenated hydrocarbons include dichloromethane, dichloroethane, dibromoethane, and the like. Examples of nitrile include acetonitrile and the like. Examples of cyclic ethers include tetrahydrofuran, dioxane, and the like. Examples of alkanol include those primary, secondary and tertiary alcohols having from one to six carbon atoms. Suitable lower alkanol solvents include methanol, ethanol, denatured spirit, n-propanol, isopropanol, n-butanol, isobutanol and t-butanol. Examples of ketones or esters include solvents such as acetone, 2-butanone, 4-methylpentan-2-one, ethyl acetate and n-butylacetate. A suitable chlorinated solvent includes one or both of dichloromethane and chloroform. Mixtures of all of these solvents are also contemplated.

DETD [0031] An organic amine or ammonia may optionally be added to the solution of **esomeprazole** salt, including **esomeprazole** magnesium, before spray drying. The organic amine may be one or more of diethylamine, triethylamine, and the like. One purpose of adding the organic amine or ammonia is to provide stability to the esomprazole during processing.

DETD [0032] If crystalline **esomeprazole** magnesium is used as a starting material it may be in the form of any of the various polymorphic forms known in the prior art including dihydrate form A, dihydrate form B, trihydrate, etc. **Esomeprazole** magnesium may be prepared by any of the known methods such as those cited in U.S. Pat. Nos. 5,714,504; 6,124,464; and 6,369,085. A solution of **esomeprazole** magnesium obtained in situ during the preparation

process may be used as such for spray drying.

DETD [0034] The resulting **amorphous** form of **esomeprazole** salt and, in particular, **esomeprazole** magnesium, may be formulated into ordinary dosage forms such as, for example, tablets, capsules, pills, solutions, etc. In these cases, the medicaments can be prepared by conventional methods with conventional pharmaceutical excipients. In addition to the common dosage forms set out above, the **amorphous** form of **esomeprazole** magnesium may also be administered by controlled release means and/or delivery devices.

DETD [0035] Further, the **amorphous esomeprazole** salt dosage forms described herein can be used in a method for treatment of gastric acid related diseases. The method of treatment includes administering to a mammal in need of treatment a dosage form that includes a therapeutically effective amount of the **amorphous** form of **esomeprazole** salt, including the **esomeprazole** magnesium salt.

DETD [0036] The present inventions are further illustrated by the following examples which are provided merely to be exemplary of the inventions and are not intended to limit the scope of the invention. Although these examples are directed to **amorphous esomeprazole** magnesium, the principles described in these examples can be applied to other salts of **amorphous esomeprazole.**

DETD PREPARATION OF **AMORPHOUS** FORM OF **ESOMEPRAZOLE** MAGNESIUM

DETD [0037] **Esomeprazole** magnesium trihydrate (200 g) was dissolved in a mixture of dichloromethane (1200 ml) and methanol (1200 ml) at 25-30° C. Any undissolved material was filtered off and triethylamine (2 ml) was added to the filtrate. The clear solution thus obtained was spray dried in a mini spray dryer (Model Buchi-190) with an inlet temperature of 65-68° C. and an outlet temperature of 22-42° C. in 2 to 3 hours. The solid was further dried under vacuum at 60-65° C. for 14 to 15 hours to yield 120 g of **esomeprazole** magnesium of **amorphous** form. X-ray powder diffraction pattern showed a plain halo, which demonstrates the **amorphous** nature of the product (FIG. 1). The following physical characteristics were obtained: Purity 99.77% by HPLC, Chiral purity 99.90% by HPLC, SOR 145.9°, Mg content 3.4.

DETD [0038] **Esomeprazole** magnesium trihydrate (20 g) was dissolved in methanol (200 ml) at 25-30° C. Any undissolved material was filtered off and triethylamine (0.2 ml) was added to the filtrate. The clear solution thus obtained was subjected to spray drying with an inlet temperature of 65-68° C. and an outlet temperature of 22-42° C. The solid was further dried under vacuum at 60-65° C. for 14 to 15 hours to yield 11.5 g of **esomeprazole** magnesium of **amorphous** form.

DETD [0039] **Esomeprazole** magnesium trihydrate (10 g) was dissolved in a mixture of dichloromethane (50 ml) and ethanol (70 ml) at 25-30° C. Any undissolved material was filtered off. The clear solution thus obtained was spray dried with an inlet temperature of 70-80° C. and an outlet temperature of 22-42° C. The solid was further dried under vacuum at 60-65° C. for 14 to 15 hours to yield 5.82 g of **esomeprazole** magnesium of **amorphous** form.

DETD [0040] **Esomeprazole** magnesium trihydrate (100 g) was dissolved in methanol (1000 ml) at 25-30° C. Any undissolved material was filtered off. The clear solution thus obtained was spray dried with an inlet temperature of 65-68° C. and an outlet temperature of 22-42° C. The solid was further dried under vacuum at 60-65° C. for 14 to 15 hours to yield 55 g of **esomeprazole** magnesium of **amorphous** form.

CLM What is claimed is:

1. An **amorphous** form of a salt of **esomeprazole.**

2. The **amorphous** form of a salt of **esomeprazole** of claim 1, wherein a cation is selected from the group consisting Na, Mg, Li, K, Ca, and N(R).sub.4, where R is a hydrogen or an alkyl group with 1-4 carbon atoms.

3. The **amorphous** form of a salt of **esomeprazole** of claim 2, wherein the cation comprises Na.

4. The **amorphous** form of a salt of **esomeprazole** of claim 2, wherein the cation comprises Mg.

5. The **amorphous** form of a salt of **esomeprazole** of claim 2, wherein the cation comprises K.

6. The **amorphous** form of a salt of **esomeprazole** of claim 2, wherein the cation comprises Ca.

7. The **amorphous** form of a salt of **esomeprazole** of claim 1, wherein the **esomeprazole** salt has the X-ray diffraction pattern of a plain halo.

9. A pharmaceutical composition comprising: a therapeutically effective amount of an **amorphous** form of a salt of **esomeprazole** ; andone or more pharmaceutically acceptable carriers, excipients or diluents.

15. The pharmaceutical composition of claim 10, wherein the **esomeprazole** salt has the X-ray diffraction pattern of a plain halo of FIG. 1.

17. A process for the preparation of a salt of the **amorphous** form of **esomeprazole**, the process comprising: preparing a solution of a salt of **esomeprazole** in one or more solvents; and recovering the salt of **esomeprazole** in the **amorphous** form from the solution thereof by the removal of the solvent.

31. The process of claim 17, wherein the salt of **esomeprazole** in an **amorphous** form is recovered from the solution by spray drying.

32. The process of claim 17, wherein the salt of **esomeprazole** in an **amorphous** form is recovered from the solution by freeze-drying.

37. The process of claim 17, wherein the **amorphous** **esomeprazole** salt obtained has the X-ray diffraction pattern of a plain halo.

L2 ANSWER 9 OF 42 USPATFULL on STN
ACCESSION NUMBER: 2004:216064 USPATFULL
TITLE: **Amorphous** hydrates of **esomeprazole** magnesium and process for the preparation thereof
INVENTOR(S): Reddy, Manne Satyanarayana, Andhra Pradesh, INDIA
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LEGAL REPRESENTATIVE: Janet I. Cord, Ladas & Parry, 26 West 61 Street, New York, NY, 10023
NUMBER OF CLAIMS: 46
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NUMBER OF DRAWINGS: 3 Drawing Page(s)
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CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A hydrate of **esomeprazole** magnesium in the form of an **amorphous** solid is provided. Methods of preparation and use of, as well as formulation containing the hydrate of **esomeprazole** magnesium in the form of an **amorphous** solid are also provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI **Amorphous** hydrates of **esomeprazole** magnesium and process for the preparation thereof

AB A hydrate of **esomeprazole** magnesium in the form of an **amorphous** solid is provided. Methods of preparation and use of, as well as formulation containing the hydrate of **esomeprazole** magnesium in the form of an **amorphous** solid are also provided.

SUMM [0002] Omeprazole and its therapeutically acceptable alkaline salts are well known inhibitors of gastric acid secretion and anti-ulcer agents. These compounds are sulfoxides and have an asymmetric center at the sulfur atom and, thus, exist as optical isomers or enantiomers. **Esomeprazole** is the (S)(-) enantiomer of omeprazole.

SUMM [0003] Omeprazole and its therapeutically acceptable alkaline salts are disclosed in EP 000 5129 and EP 124,495, respectively. U.S. Pat. No. 6,162,816 discloses crystalline Form A and crystalline Form B of **esomeprazole** and characterizes them by X-ray powder diffraction. U.S. Pat. No. 5,693,818 discloses various salts of omeprazole enantiomers, including **esomeprazole** magnesium. U.S. Pat. No. 6,369,085 discloses a particular crystalline form of **esomeprazole** magnesium trihydrate.

SUMM [0004] A number of drugs have been found to exhibit desirable dissolution characteristics and, in some cases, desirable bioavailability patterns when used in a specific solid form, e.g., as an **amorphous** or crystalline solid. Therefore, there is a continuing need for new solid forms of **esomeprazole** and methods of their preparation.

SUMM [0005] In one aspect, the invention provides a compound, which is a hydrate in the form of an **amorphous** solid, having the formula ##STR1##

SUMM [0006] where one of R.sup.1 and R.sup.2 is hydrogen and the other is methoxy; A is an alkaline earth or alkali metal; and m and n are 1 or 2. Preferably, the compound of this aspect of the invention is a hydrate of **esomeprazole** magnesium, which is in the form of an **amorphous** solid. Various embodiments and variants are provided.

SUMM [0007] In according with another aspect, the invention provides a

composition that includes **esomeprazole** magnesium as a solid, wherein at least 80% by weight of the solid **esomeprazole** magnesium is a hydrate of **esomeprazole** magnesium in the form of an **amorphous** solid. Various embodiments and variants are provided.

DRWD [0009] FIG. 1 is an X-ray powder diffractogram for a batch of bulk powder which is a hydrate of **esomeprazole** magnesium in the form of an **amorphous** solid.

DRWD [0010] FIG. 2 shows a TGA thermogram for a batch of bulk powder which is a hydrate of **esomeprazole** magnesium in the form of an **amorphous** solid.

DRWD [0011] FIG. 3 shows a DSC thermogram for a batch of bulk powder which is a hydrate of **esomeprazole** magnesium in the form of an **amorphous** solid.

DETD [0017] The term "pharmaceutical composition" is intended to encompass a product comprising the active ingredient(s), pharmaceutically acceptable excipients that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing the **amorphous** solid described herein, additional active ingredient(s), and pharmaceutically acceptable excipients.

DETD [0025] where one of R.sup.1 and R.sup.2 is hydrogen and the other is methoxy; A is an alkaline earth or alkali metal; and m and n are 1 or 2, the compound being a hydrate and being in the form of an **amorphous** solid. Examples of A include lithium, sodium, potassium, calcium, and magnesium. m and n should be equal if a neutral salt is desired, if they are not equal the compound will carry a net charge. One salt may be converted to the salt of another cation by conventional methods of exchanging the cation, for example on a cation exchange resin saturated with the desired cation, or by taking advantage of differential solubility of the salts.

DETD [0026] In a preferred embodiment, the compound of the formula (I) preferably has m and n that are both 2, and A is magnesium, i.e., the compound is a magnesium salt of **esomeprazole.** **Esomeprazole** ((S)(-)5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulphinyl]-1H-benzimidazole; the S(-)enantiomer of omeprazole), as well as its salts, is an active gastric acid secretion inhibitor. Preferably, the hydrate of **esomeprazole** magnesium is a trihydrate, which contains approximately three water molecules. FIG. 1 shows an X-ray diffractogram of one batch of solid **esomeprazole** magnesium obtained by the inventors (the process of making the compounds described herein is described in greater details below). An XRD pattern that shows no significant peaks is characteristic of an **amorphous** solid. As seen in reference to FIG. 1, the XRD pattern shows no peaks and has a plain halo, demonstrating the **amorphous** nature of the solid. The x-ray powder diffractogram was measured on a Bruker Axs, D8 Advance X-ray Powder diffractometer with Cu K alpha-1 radiation source.

DETD [0027] In another aspect, the invention provides a composition including **esomeprazole** magnesium as a solid, in which at least 80%, preferably 90%, more preferably 95%, and most preferably 99% by weight of the solid **esomeprazole** magnesium is a hydrate of **esomeprazole** magnesium in the form of an **amorphous** solid. The remainder of the **esomeprazole** magnesium in the composition, e.g., 20%, preferably 10%, more preferably 5%, and most preferably 1% or less of the total weight of **esomeprazole** magnesium, may be one or more crystalline forms of **esomeprazole**

magnesium. In one embodiment of this composition, the solid **esomeprazole** magnesium hydrate is substantially free from crystalline forms of **esomeprazole** magnesium. In yet another embodiment, in addition to a hydrate of **esomeprazole** magnesium in the form of an **amorphous** solid, the composition includes at least a small amount of crystalline forms of **esomeprazole** magnesium. In a non-limiting example, the composition includes 95% of the hydrate of **esomeprazole** magnesium in the form of an **amorphous** solid and at least 1% of any crystalline form of **esomeprazole** magnesium. In another non-limiting example, the composition includes at least 80% of the hydrate of **esomeprazole** magnesium in the form of an **amorphous** solid and at least 5% of other crystalline forms of **esomeprazole** magnesium. All compositions, in 0.1% increments, which include at least 80% of the hydrate of **esomeprazole** magnesium in the form of an **amorphous** solid and at least 1% of crystalline forms of **esomeprazole** magnesium, are contemplated. All percentages are based upon the total amount of the solid **esomeprazole** magnesium in the composition.

DETD [0028] The preferred form of the composition of this aspect of the invention is a solid powder of bulk **esomeprazole** magnesium for use as an active pharmaceutical ingredient. This powder composition has a moisture content, which is preferably from about 2% to about 10% as measured by the Karl Fischer method, and more preferably from about 7% to about 8%. Moisture content may be measured by any accepted technology, for example by using Karl Fischer reagent (KF) and an appropriate instrument (goniometer) such as a Mettler DL-35, a Scintag PAD V, a Brukker D5000, or by thermogravimetric analysis using moisture analysis instruments such as the Mettler DSC20, TG50, and TC10A. FIG. 2 shows a TGA thermogram for a batch of bulk powderwhich is a hydrate of **esomeprazole** magnesium in the form of an **amorphous** solid. FIG. 3 shows a DSC thermogram for a batch of bulk powder which is a hydrate of **esomeprazole** magnesium in the form of an **amorphous** solid.

DETD [0029] To determine the relative amounts of **amorphous** and crystalline components in the composition of this aspect of the invention, one suitable analytical methodology is X-ray powder diffraction (XRD). XRD methodology is capable of providing both qualitative and quantitative information about compounds present in a solid sample. XRD is adaptable to quantitative applications because the intensities of the diffraction peaks of a given compound in a mixture are proportional to the fraction of the material in the mixture. By measuring the intensity of the diffraction lines and comparing them with standards, it is possible to make a quantitative analysis of crystalline mixtures.

DETD [0030] As explained above, **amorphous** solids have no characteristic peaks. In contrast, each crystalline solid is arranged in a set of planes separated by interplanar space d, and exhibits a diffraction pattern with a unique set of peaks generated when x-rays strike a plane at angle theta and are diffracted at the same angle, thus the 2 theta angle is determined by the spacing between a particular set of planes. The identification of a crystalline solid is based upon peaks in the XRD pattern being tabulated in terms the diffraction angle 2 theta (or d-spacing) and their relative intensities. Identification of a crystal form of a compound should be based primarily on observed 2 theta angles with lesser importance being attributed to relative peak intensities. Slight variations in observed 2 theta angles or d-spacing values are expected based on the specific diffractometer employed and the sample preparation technique.

DETD [0031] Different quantitative techniques are available. For example, two methods may be used to analyze XRD quantitatively: the Internal Standard Method and the External Standard Method. The Internal Standard Method is

the preferred procedure for analyzing powdered systems. This method measures a known quantity of a reference powder which is added to an unknown powder. The mass absorption coefficient of the mixture need not be known in advance. Any number of constituents in the mixture may be quantified independently, including the **amorphous** (non-crystalline) components. The External Standard Method is used to analyze solid systems when the mass absorption co-efficient is known. It allows the quantification of one or more components in a system, which may contain an **amorphous** fraction. The percent composition of a crystalline compound can be determined in an unknown composition. The XRD patterns of an unknown composition can be compared to a known standard containing pure crystalline compound to identify the percent ratio of the crystalline form of the compound. This is done by comparing the relative intensities of the peaks from the diffraction pattern of the unknown composition with a calibration curve based on the XRD pattern for the strongest peak derived from the XRD pattern of a pure crystalline sample of the compound. The peak intensities are reported as intensities relative to the peak intensity of the strongest peak ("the 100% peak"). The calibration curve may be created in a manner known to those of skill in the art. For example, five or more artificial mixtures of **amorphous** and crystalline forms of crystalline compound in different amounts, may be prepared. As an example, such mixtures may contain, 2%, 5%, 7%, 8%, and 10% of crystalline compound, with the remainder being the **amorphous** form of the salt. Then, XRD patterns are obtained for each artificial mixture using standard XRD techniques. Slight variations in peak positions, if any, may be accounted for by adjusting the location of the peak to be measured. The intensities of the 100% peak(s) for each of the artificial mixtures are then plotted against the known weight percentages of the crystalline form. The resulting plot is a calibration curve that allows determination of the amount of crystalline compound in an unknown sample. For the unknown mixture of crystalline and **amorphous** compounds, the intensities of the 100% peak(s) in the mixture, relative to an intensity of this peak in a calibration mixture, may be used to determine the percentage of the crystalline form in the composition, with the remainder determined to be the **amorphous** material.

DETD [0032] In order to determine the relative amount of **amorphous** to crystalline solid in compositions of this invention, XRD information may be used to create the calibration curve(s) described above. For use in this comparative analysis, XRD patterns of crystalline forms of **esomeprazole** are obtainable by known methods of measurement. In addition, the XRD data for crystalline Form I **esomeprazole** magnesium trihydrate is disclosed in U.S. Pat. No. 6,369,085, which is incorporated by reference for this purpose. The XRD data for crystalline form II **esomeprazole** magnesium trihydrate were obtained by the inventors:

2-theta value	Relative Intensity (%)
4.824	100.0
18.471	81.7
5.552	43
14.16	28.1
12.104	25.3
8.608	22.3
21.089	21.5
7.411	18.8

DETD [0033] In another aspect, the invention provides a process for making a hydrate of **esomeprazole** magnesium in the form of an **amorphous** solid by a) providing **esomeprazole** magnesium

in an alcohol-containing solvent, b) contacting the **esomeprazole** magnesium in the alcohol-containing solvent with water so that a solid mass separates, and c) isolating the separated solid mass (for example by filtration), which is the hydrate of **esomeprazole** magnesium in the form of an **amorphous** solid. The starting materials and reagents used in this process are commercially available and/or may be readily synthesized by a skilled person, unless otherwise indicated. **Esomeprazole** base may be made as described in the Reference Example below from omeprazole sodium, the preparation of which is well known in the art. See in addition U.S. Pat. Nos. 6,162,816 and 5,693,818, which are incorporated herein by reference.

DETD [0035] Certain operational steps are well known in the art and, unless otherwise indicated, any known method for performing these functions may be used in the processes of this invention. For example, solvents may be removed by distillation in atmosphere or under vacuum. Drying may be accomplished by evaporation, spray drying, drying under vacuum, and freeze-drying. Stirring means any method for blending or mixing a reaction mixture. Reagents and/or reaction mixtures may be combined by adding one to the other, for example, water may be poured into a reaction mixture. In general the methods of this invention involve various such steps, e.g. combining **esomeprazole** base with a suitable counterion such as magnesium, to form **esomeprazole** magnesium, hydrating the **esomeprazole** magnesium by combining with water to form an **esomeprazole** magnesium hydrate, removing organic impurities and excess magnesium, and drying the **esomeprazole** magnesium hydrate (preferably trihydrate) to obtain a hydrate of **esomeprazole** magnesium in the form of an **amorphous** solid.

DETD [0036] In one embodiment of this aspect of the invention, **esomeprazole** magnesium is provided by suspending magnesium metal in an alcohol-containing solvent in the presence of a haloalkane and adding **esomeprazole** base (which may itself be dissolved in an alcohol-containing solvent). Preferred haloalkanes are dichloromethane, dichloromethane (in particular 1,2-dichloroethane) and trichloromethane (chloroform); most preferably, dichloromethane. The process then continues by contacting with water as described above. Contacting with water may be accomplished by pouring water into the **esomeprazole** magnesium solution, or by pouring the **esomeprazole** magnesium solution into water, or by other conventional methods. The preferred amounts of alcohol-containing solvent and of water in milliliters (ml) may be determined relative to the amount of the starting **esomeprazole** magnesium (i.e., the **esomeprazole** magnesium in the alcohol-containing solvent provided in the first step of the process) in grams (g). The amount of alcohol-containing solvent is preferably about 5 ml to about 10 ml per 1 gram of the starting **esomeprazole** magnesium, preferably about 6 to about 7 ml. The amount of water is preferably about 5 ml to about 25 ml per 1 gram of the starting **esomeprazole** magnesium, preferably, about 18 ml.

DETD [0038] In another embodiment of this aspect of the invention, the **esomeprazole** magnesium is provided in methanol or a mixture of methanol with acetone and water, preferably in an amount of about 5 ml to about 10 ml per 1 gram of the starting **esomeprazole** magnesium. The **esomeprazole** magnesium provided in methanol or a mixture of methanol with acetone and water is then concentrated to about 80% of its original volume, reducing the ratio of the solvent (the methanol or the mixture of methanol with acetone and water) to the starting **esomeprazole** magnesium. After the concentrated solution of the **esomeprazole** magnesium in the alcohol-containing solvent is contacted with water so that a solid mass separates, it is helpful to filter the solid mass and wash it with water. It is possible to seed **esomeprazole** magnesium in the alcohol-containing solvent (for example methanol or a mixture of

methanol with acetone and water) with **esomeprazole** magnesium in the form of an **amorphous** solid, for example by adding the latter to the water with which the former is contacted.

DETD [0039] One specific variant of this aspect of the invention involves dissolving magnesium at a temperature of 30° C. to 60° C. in a straight or branched lower alkanol (one to four carbons) solvent, adding haloalkane (one to three carbons) solvent, cooling to 0° C. to 15° C., adding **esomeprazole** base in a straight or branched lower alkanol solvent to generate a reaction mass, decomposing the reaction mass by pouring the mass into water and stirring for one to two hours, filtering out the resulting solid by conventional methods, suspending the solid obtained by filtering in a solvent such as acetone and stirring for one to two hours, filtering out the solid from the suspension by conventional methods (to remove excess magnesium), dissolving the solid resulting from the filtering in a straight or branched lower alkanol solvent and filtering the solution a straight or branched lower alkanol solvent, distilling off the solvent from the filtrate under reduced pressure, suspending the resulting solid in a solvent such as ethyl acetate (to crystallize solid), then either filtering by conventional methods; or adding **esomeprazole** magnesium in the form of an **amorphous** solid as seeding material and cooling to a temperature of 0° C. to 20° C. and then filtering by conventional methods, and drying the resulting solid at a temperature of 3° C. to 100° C., preferably 60° C., to obtain a hydrate of **esomeprazole** magnesium in the form of an **amorphous** solid.

DETD [0040] In another aspect, the invention provides part pharmaceutical compositions which include a hydrate of **esomeprazole** magnesium in the form of an **amorphous** solid. Pharmaceutical compositions generally contain, in addition to the active compound or compounds, one or more carriers (also called excipients) which ordinarily lack pharmaceutical activity per se, but have various useful properties which can, for example, enhance the stability, sterility, bioavailability, and ease of formulation of a pharmaceutical composition. These carriers are pharmaceutically acceptable, meaning that they are not harmful to humans or animals when taken appropriately and are compatible with the other ingredients in a given formulation. The carrier may be solid, semi-solid, or liquid, and may be formulated with the compound in bulk, but ultimately in the form of a unit-dose formulation (i.e., a physically discrete unit containing a specific amount of active ingredient) such as a tablet or capsule.

DETD [0048] Also part of this invention are methods of treatment using one or more of the compounds of this invention and the pharmaceutical compositions of this invention. In particular, a hydrate of **esomeprazole** magnesium in the form of an **amorphous** solid may be administered to a subject in an amount effective to reduce secretion of gastric acid by that subject. Although it is possible to use compounds and compositions of this invention to prevent secretion of gastric acid by establishing a dosage level effective to do so, such treatment would only be applicable in special cases, since to alleviate or eliminate most of the conditions discussed above which are treated with the compounds of this invention, gastric acid secretion should not be eliminated altogether, but only reduced in amount or duration. In general, the treatment may be determined to alleviate, to eliminate, or to prevent a given condition based on factors determinable by a skilled physician as discussed below in the context of determining an effective amount for dosage. Further, the compounds of this invention may be administered to a subject for treating a disorder caused by gastric acid secretion by administering to a subject an amount effective to reduce gastric acid secretion by said subject.

DETD Preparation of **Esomeprazole** Base

DETD [0054] Magnesium metal (1.55 grams) was suspended in methanol (111 ml),

dichloromethane (3.7 ml) was added, and stirred for 1-2 hours at a temperature of 50-60° C. The mass was cooled to a temperature of 5-10° C. and **esomeprazole** base (37.0 grams, prepared as per reference example) and methanol (111.0 ml) were added accompanied by stirring for 15-30 minutes. The reaction mass was decomposed by pouring into water (666 ml) at a temperature of 5-1° C. over a period of 45-60 minutes. The reaction mass was further stirred for 30-45 minutes to separate the solid mass. The solid mass was filtered, washed with water (222 ml) and suck dried under vacuum. The wet solid was suspended in acetone (148 ml) and stirred for 15-30 minutes at a temperature of 5-1° C. The solid mass was filtered and washed with acetone (37 ml). The compound obtained was dissolved in methanol (222 ml) and the solution filtered to separate the excess magnesium. The solvent was distilled off from the distillate at a temperature of 35-40° C. under reduced pressure to get the residual mass.

DETD [0055] The residual mass was crystallized in ethyl acetate (100 ml) at a temperature of 25-35° C. and stirred for 10-15 minutes. The crystallized mass was further stirred at a temperature of 0-5° C. for 1-2 hours. The crystallized solid was filtered, washed with ethyl acetate (50 ml) and dried at 60-65° C. to afford a hydrate of **esomeprazole** magnesium in the form of an **amorphous** solid.

DETD [0057] **Esomeprazole** magnesium in methanol solution (660 ml, which is equivalent to 100 grams of **esomeprazole** base, prepared as per Example 1) and acetone (30 ml) and water (30 ml) were stirred for 10-15 minutes at room temperature. Then the reaction mixture was allowed to settle and the unwanted material was filtered off. The filtrate was distilled to 80% of its initial volume. The concentrated reaction mass was poured slowly in to water (750 ml) under stirring. The resulting reaction mass was cooled to a temperature of 0-5° C. and stirred to isolate the solid. Then the isolated solid was filtered, washed with water (300 ml) and dried at a temperature of 60-70° C. to yield a hydrate of **esomeprazole** magnesium in the form of an **amorphous** solid. KF was measured on Mettler DL-35 instrument using Karl Fischer reagent.

DETD [0059] A methanolic solution of **esomeprazole** magnesium (660 ml, which is equivalent to 100 grams of **esomeprazole** base, prepared as per Example 1) was concentrated to 80% of its initial volume under reduced pressure. The concentrated reaction mass was poured slowly in to water (750 ml) containing the **amorphous** form of **esomeprazole** magnesium (0.1 gram) as seeding material at a temperature of 0-5° C. The resulting reaction mass was stirred to isolate the solid. Then the isolated solid was filtered, washed with water (300 ml) and dried at a temperature of 60-70° C. to yield a hydrate of **esomeprazole** magnesium in the form of an **amorphous** solid. KF was measured on Mettler DL-35 instrument using Karl Fischer reagent.

DETD [0061] A methanolic solution of **esomeprazole** magnesium (100 ml, which is equivalent to 60 grams of **esomeprazole** base, prepared as per Example 1) was concentrated to 80% of its initial volume under reduced pressure. The concentrated reaction mass was poured slowly in to ethyl acetate (500 ml) containing **amorphous** form of **esomeprazole** magnesium (0.1 gram) as seeding material at a temperature of 0-5° C. The resulting reaction mass was stirred to isolate the solid. Then the isolated solid was filtered, washed with ethyl acetate (100 ml) and dried at a temperature of 60-70° C. to yield a hydrate of **esomeprazole** magnesium in the form of an **amorphous** solid. KF was measured on Mettler DL-35 instrument using Karl Fischer reagent.

CLM What is claimed is:

1. A compound of the formula ##STR3## wherein one of R.sup.1 and R.sup.2 is hydrogen and the other is methoxy; A is an alkaline earth or

alkali metal; and m and n are 1 or 2; said compound being a hydrate and being in the form of an **amorphous** solid.

4. A compound which is a hydrate of **esomeprazole** magnesium, said compound being in the form of an **amorphous** solid.

6. A composition which comprises **esomeprazole** magnesium as a solid, wherein at least 80% by weight of the solid **esomeprazole** magnesium is a hydrate of **esomeprazole** magnesium in the form of an **amorphous** solid.

7. The composition of claim 6, wherein said hydrate of **esomeprazole** magnesium is a trihydrate.

8. The composition of claim 6, wherein at least 90% by weight of the solid **esomeprazole** magnesium is a hydrate of **esomeprazole** magnesium in the form of an **amorphous** solid.

9. The composition of claim 6, wherein at least 95% by weight of the solid **esomeprazole** magnesium is a hydrate of **esomeprazole** magnesium in the form of an **amorphous** solid.

10. The composition of claim 6, wherein at least 99% by weight of the solid **esomeprazole** magnesium is a hydrate of **esomeprazole** magnesium in the form of an **amorphous** solid.

11. The composition of claim 6, which is a solid powder of bulk **esomeprazole** magnesium for use as an active pharmaceutical ingredient.

14. The composition of claim 6, wherein 20% or less by weight of the solid **esomeprazole** magnesium is in crystalline form.

15. The composition of claim 6, wherein 10% or less by weight of the solid **esomeprazole** magnesium is in crystalline form.

16. The composition of claim 6, wherein 5% or less by weight of the solid **esomeprazole** magnesium is in crystalline form.

17. The composition of claim 6, wherein 1% or less by weight of the solid **esomeprazole** magnesium is in crystalline form.

18. The composition of claim 6, wherein said solid **esomeprazole** magnesium is substantially free of crystalline forms of **esomeprazole** magnesium.

19. A process for making a hydrate of **esomeprazole** magnesium in the form of an **amorphous** solid, said process comprising: a) providing **esomeprazole** magnesium in an alcohol-containing solvent; b) contacting said **esomeprazole** magnesium and said alcohol-containing solvent with water so that a solid mass separates; and c) isolating said separated solid mass, which is the hydrate of **esomeprazole** magnesium in the form of an **amorphous** solid.

20. The process of claim 19, wherein the **esomeprazole** magnesium is provided by suspending magnesium metal in an alcohol-containing solvent in the presence of a haloalkane and adding **esomeprazole** base thereto.

25. The process of claim 19 wherein the amount of alcohol-containing solvent is about 5 ml to about 10 ml per 1 gram of the starting **esomeprazole** magnesium.

26. The process of claim 19, wherein the amount of water is about 5 ml to about 25 ml per 1 gram of the starting **esomeprazole** magnesium.

27. The process of claim 26, wherein the amount of water is about 18 ml per 1 gram of the starting **esomeprazole** magnesium.

34. A process for making a hydrate of **esomeprazole** magnesium in the form of an **amorphous** solid, said process comprising: a) providing **esomeprazole** magnesium in methanol; b) contacting said **esomeprazole** magnesium in methanol with water so that a solid mass separates; c) isolating said solid mass by filtration; d) washing said solid mass; e) dissolving said solid mass in methanol and filtering the solution so formed to separate excess magnesium solids; f) removing solvent from the solution to obtain isolated residual mass; g) re-precipitating said isolated residual mass from ethyl acetate, and h) drying said isolated residual mass, which is the hydrate of **esomeprazole** magnesium in the form of an **amorphous** solid.

35. The process of claim 34, wherein the **esomeprazole** magnesium is provided by suspending magnesium metal in methanol in the presence of dichloromethane and adding **esomeprazole** base.

37. The process of claim 36, wherein said providing step includes dissolving said starting **esomeprazole** magnesium in methanol or in a mixture of methanol with acetone and water.

38. The process of claim 36, wherein the amount of methanol or mixture of methanol with acetone and water is about 5 ml to about 10 ml per 1 gram of the starting **esomeprazole** magnesium.

39. The process of claim 38, wherein said **esomeprazole** magnesium provided in said methanol or mixture of methanol with acetone and water is concentrated to about 80% of the original volume before contacting with water.

41. The process of claim 39, further comprising seeding said **esomeprazole** magnesium in said methanol or mixture of methanol with acetone and water with **esomeprazole** magnesium in the form of an **amorphous** solid.

43. A pharmaceutical composition comprising the compound of Formula 1 in the form of an **amorphous** solid and a pharmaceutically acceptable carrier.

44. A pharmaceutical composition comprising a hydrate of **esomeprazole** magnesium in the form of an **amorphous** solid, and a pharmaceutically acceptable carrier.

45. A method for reducing gastric acid secretion in a subject which comprises administering to the subject an amount of the compound of Formula 1 in the form of an **amorphous** solid effective to reduce gastric acid secretion by said subject.

46. A method for reducing gastric acid secretion in a subject which comprises administering to the subject an amount of a hydrate of

esomeprazole magnesium in the form of an **amorphous** solid effective to reduce gastric acid secretion by said subject.

L2 ANSWER 10 OF 42 USPATFULL on STN

ACCESSION NUMBER:	2004:203995 USPATFULL
TITLE:	Alkoxy substituted benzimidazole compounds, pharmaceutical preparations containing the same, and methods of using the same
INVENTOR(S):	Whittle, Robert R., Wilmington, NC, UNITED STATES Sancilio, Frederick D., Wilmington, NC, UNITED STATES Stowell, Grayson Walker, Wilmington, NC, UNITED STATES Jenkins, Douglas John, Wilmington, NC, UNITED STATES Whittall, Linda B., Wilmington, NC, UNITED STATES

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PATENT INFORMATION:	US 2004157887	A1	20040812
APPLICATION INFO.:	US 2004-769021	A1	20040202 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2003-434259, filed on 8 May 2003, GRANTED, Pat. No. US 6706737 Continuation of Ser. No. US 2002-189659, filed on 3 Jul 2002, GRANTED, Pat. No. US 6667321 Continuation of Ser. No. US 2002-57659, filed on 25 Jan 2002, GRANTED, Pat. No. US 6444689 Continuation of Ser. No. US 2000-645145, filed on 24 Aug 2000, GRANTED, Pat. No. US 6369087 Continuation-in-part of Ser. No. US 2000-519976, filed on 7 Mar 2000, GRANTED, Pat. No. US 6262085

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PRIORITY INFORMATION:	US 1999-150878P	19990826 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	MYERS BIGEL SIBLEY & SAJOVEC, PO BOX 37428, RALEIGH, NC, 27627
NUMBER OF CLAIMS:	64
EXEMPLARY CLAIM:	1
LINE COUNT:	4121

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compounds represented by formula (Ia) are disclosed by the invention, along with compositions and complexes thereof, optionally in combination with compounds of formula (Ib). Pharmaceutical formulations and methods of making and using such compounds are also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM [0009] The teachings regarding the methods of making omeprazole as referred to in these references, salts thereof, enantiomers thereof, and salts of the enantiomers, as well as formulations which may include these compounds, all rely on the chemical structure of omeprazole being accurately determined and the referenced compound or compounds being consistently prepared using the referenced techniques. More specifically, a methoxy group on the benzimidazole ring has been explicitly stated in the literature to be present at the 5-position, in omeprazole, a racemic mixture, and an optically pure isomer of omeprazole designated as **esomeprazole** or **s-omeprazole**. Applicants have now unexpectedly discovered the complexity of omeprazole and the relative bioactivity of each of its previously undiscovered and undisclosed attributes. More specifically, Applicants have confirmed that the methods of the prior art do not yield a single compound having the methoxy group in the 5-position on the benzimidazole ring as previously taught, nor do all of the methods of

the prior art yield consistent results. In fact, omeprazole as conventionally referred to as a bulk drug substance (in its solid state) has been discovered to be present in the form of two pharmaceutically active compounds having the methoxy group on the benzimidazole ring at the 6- and 5-positions. Additionally, Applicants have discovered the presence of a second chiral location at the pyridine ring plane in each of the two compounds such that each compound has two positional isomers and four diastereomers. Therefore, the present invention provides these individual compounds, along with any salts, hydrates, solvates, combinations thereof, and polymorphs thereof, compositions of the above, and methods of making the same that are not taught or suggested by the prior art, pharmaceutical formulations of the compounds, compositions, and complexes of the present invention, and methods for using the same.

SUMM [0071] Accordingly, methods of the present invention provide for improved biological activity/efficacy (e.g. inhibition of gastric acid secretions and, thus, treatment of gastric acid disturbances in mammals, including humans) of pharmaceutically active compounds omeprazole and **esomeprazole**, as presently known in the art, comprising administering to such mammals in need of treatment a non-toxic, therapeutically effective amount of any composition of the present invention comprising compounds or compositions of the present invention having individual diastereomers comprising S.sub.xa--R.sub.4q; S.sub.xa--R.sub.4z; S.sub.xb--R.sub.4q; or S.sub.xb--R.sub.4z, or one or more pharmaceutically acceptable salts, solvates, hydrates, or combinations thereof. Also provided are such methods wherein said compounds or complexes of the present invention having said selected individual diastereomer pair essentially free of compounds of the present invention having diastereomer pairs other than said selected individual diastereomers. A preferred diastereomer is S.sub.xa--R.sub.4q, and an especially preferred diastereomer is S.sub.xa--R.sub.4z.

SUMM [0079] In another aspect, the invention also provides compositions of active pharmaceutical ingredient ("API") comprising any of the compounds, compositions, or complexes of the present invention, each of which may be present in crystalline form, in part or in whole. Advantageously, each such compositions and/or complexes comprising compounds represented by formula (Ia) may also include any one or more of the specific compounds represented by formulae (Iai), (Iaii), (Iaiii), and (Iaiv), or pharmaceutically acceptable salts, solvates, hydrates, polymorphs, or combinations thereof, whether in crystalline form, **amorphous** form, or a combination thereof. Each can be used as the bases for any such API composition.

SUMM [0139] Any of such composition embodiments comprising any of the compounds represented by formulae (Ia) and (Ib), individual species of compounds (Iai)-(Ibi), (Iaii)-(Ibii), (Iaiii)-(Ibiii), and (Iaiv)-(Ibiv), diastereromers thereof, or one or more pharmaceutically acceptable salts, solvates, hydrates, or combinations thereof, may be present in crystalline form, **amorphous** form, or combinations thereof.

SUMM [0140] The invention also provides compositions of active pharmaceutical ingredient ("API") comprising any of the above composition embodiments. Advantageously, any of the compositions comprising compounds represented by formulae (Ia) and (Ib) may also comprise any of the specific compositions represented by formulae (Iai)-(Ibi); (Iaii)-(Ibii); (Iaiii)-(Ibiii); and (Iaiv)-(Ibiv) or one or more pharmaceutically acceptable salts, solvates, hydrates, polymorphs, or combinations thereof, whether in crystalline form, **amorphous** form, or a combination thereof, can be used in any such API compositions.

SUMM [0143] Additionally, when using such processes represented in the prior art, negligible or trace amounts of previously unknown compounds are formed as described herein. For example, in the preparation of such composition as referenced in the immediately preceding paragraph, compounds having the previously unknown diastereomers S.sub.xa--R.sub.4q and S.sub.xb--R.sub.4z, are formed with varying and inconsistent ratios of compounds represented by formulae (Ia) and (Ib). Also formed in trace quantities, and typically in **amorphous** form, are compounds represented by formulae (Ia) and (Ib) having the previously unknown diastereomers S.sub.xa--R.sub.4q and S.sub.xb--R.sub.4q.

SUMM [0145] Accordingly, the processes taught in the prior art for the preparation of "omeprazole" as well as "**esomeprazole**" (the intended S-isomer of "omeprazole") provide quantities of previously unknown and unrecognized compounds having pharmaceutical activity, or that are used as intermediates in the preparation of pharmaceutically active compounds of the present invention, or that are used as prodrugs that convert to the active metabolite in vivo. Furthermore, many such processes do not invariably provide the same result when conducted as taught in the prior art

SUMM [0172] By employing the above method(s) of obtaining the compound represented by formula (Ia) in solid state, one obtains the (-) and (+) enantiomers as a racemic mixture, with these enantiomers including various amounts of diastereomers as set forth herein. In one embodiment, Applicants have discovered that the (-) and (+) enantiomers may be predominantly present as the S.sub.xa--R.sub.4q and S.sub.xb--R.sub.4z diastereomers respectively. Although not intending to be bound by theory, in this embodiment, the two molecules (i.e., compounds of formulae (Ia) and (Ib)) co-crystallize in a centric space group in which the molecules are related to each other through a center of inversion and linked by hydrogen bonding from the amine hydrogens to the sulfoxide oxygens. The R.sub.4 methoxy methyl is directed towards the center of the bridged complex. Examination of the contact distances in the region where the other methoxy methyl would presumably reside demonstrates that there is not adequate space within the lattice for the other diastereomers (S.sub.xa--R.sub.4z and S.sub.xb--R.sub.4q) to coexist. In this embodiment, the compound represented by formula (Ia) may comprise about 99 percent (w/w) of the S.sub.xb--R.sub.4z and S.sub.xa--R.sub.4q diastereomers and the remaining percentage of other components which may include, for example, the diastereomers S.sub.xa--R.sub.4. and S.sub.xb--R.sub.4q, generally in **amorphous** form.

SUMM [0178] Although not intending to be bound by theory, such compounds of formula (Ia) are believed to be crystalline with little **amorphous** content. However, when grinding is applied to a sclid sample comprising the compound of formula (Ia), and in a preferred embodiment the compounds of formulae (Ia) and (Ib), an increase in the **amorphous** character of the sample is believed to result along with an increase in the amount of compound of formula (Ib). Again, not intending to be bound by theory, it is believed that the sample undergoes a solid state transformation and "recrystallizes" or transforms over a relatively short period of time from the more **amorphous** state to a more crystalline state subsequent to grinding. Nonetheless, it is believed that by performing multiple grinding steps in sequence, (i.e., grinding followed by relaxation followed by grinding) one may obtain a solid sample that becomes more **amorphous** in character and hence comprises a greater amount of the compound of the formula (Ib) as opposed to a sample that has experienced a lesser amount of grinding.

SUMM [0180] The structure of the compound of formula (Ib) can be confirmed by solid state techniques such as, for example, X-ray powder diffraction patterns, Raman, FTIR, solid state NMR, and thermal analysis, of the ground material and the unground material. For example, comparison of the two powder patterns showed distinct decreases in intensity, broadening of the peaks, and an increase in the **amorphous** nature for the ground material. The ground material showed a powder pattern that is more consistent with the proposed more **amorphous** nature of the compound of formula (Ib), e.g., 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

SUMM [0297] The following examples are intended to illustrate the invention, and are not to be construed as limiting the scope of the invention. For the purposes of the examples, the phrase "(5)6-methoxy 2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole" refers to a combination of, preferably a co-crystallized mixture, (with or without an amount of **amorphous** compounds), of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole and 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole, each as determined and referenced herein.

L2 ANSWER 11 OF 42 USPATFULL on STN

ACCESSION NUMBER:	2004:197408 USPATFULL			
TITLE:	Benzylaminopyrimidines			
INVENTOR(S):	Grundler, Gerhard, Konstanz, GERMANY, FEDERAL REPUBLIC OF			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2004152714	A1	20040805	
	US 6818642	B2	20041116	
APPLICATION INFO.:	US 2004-477622	A1	20040323	(10)
	WO 2002-EP5266		20020514	
	NUMBER		DATE	
PRIORITY INFORMATION:	EP 2001-112226		20010518	
	DE 2001-139825		20010814	
	DE 2001-162319		20011219	
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	APPLICATION			
LEGAL REPRESENTATIVE:	Gary M Nath, Nath & Associates, Sixth Floor, 1030 15th Street NW, Washington, DC, 20005			
NUMBER OF CLAIMS:	20			
EXEMPLARY CLAIM:	1			
LINE COUNT:	1239			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Benzylaminopyrimidine compounds of a certain general formula I, in which the substituents and symbols are as defined in the description, are suitable for controlling Helicobacter bacteria.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD [0292] In analogy to the method described in example A1, 19.3 g (0.12 mol) of 4-amino-5-chloro-2,6-dimethylpyrimidine, 28.3 g (0.12 mol) of 3-benzyloxybenzyl chloride and 5.2 g (0.13 mol) of sodium hydride (60% suspension in liquid paraffin) are reacted in a total of 170 ml of N-methylpyrrolidone. After chromatography on silica gel (mobile phase:toluene/dioxane=20:1), the title compound is isolated as an **amorphous** solid. Yield: 23.8 g (56% of theory). .sup.1H NMR spectrum (CDCl.sub.3, δ ppm): 7.4-7.1 (m, 6H), 7.0-6.8 (m, 3H),

5.56 (tb, NH), 5.05 (s, 2H), 4.67 (d, 2H), 2.49 (s, 3H), 2.41 (s, 3H)

DETD [0330] Examples of gastric acid neutralizers Include sodium bicarbonate or other antacids (such as aluminum hydroxide, magnesium aluminate or magaldrate). Examples of gastric acid secretion inhibitors that may be mentioned include H.sub.2 blockers (e.g., cimetidine, ranitidine), H.sup.+/K.sup.+ ATPase Inhibitors (e.g., lansoprazole, omeprazole, **esomeprazole**, rabeprazole or, in particular, pantoprazole) and what are known as reversible H.sup.+/K.sup.+ ATPase inhibitors (compounds as disclosed, for example, in international patent applications WO 00/11000, WO 00/10999, WO 99/55706, WO 99/55705 or WO 98/37080, and structurally similar compounds).

L2 ANSWER 12 OF 42 USPATFULL on STN

ACCESSION NUMBER: 2004:152209 USPATFULL

TITLE: Substituted aryl compounds as novel cyclooxygenase-2 selective inhibitors, compositions and methods of use

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Gaston, Ricky D., Malden, MA, UNITED STATES

PATENT ASSIGNEE(S): NitroMed, Inc., Bedford, MA, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004116431	A1	20040617
	US 6825185	B2	20041130
APPLICATION INFO.:	US 2003-730979	A1	20031210 (10)

RELATED APPLN. INFO.: Division of Ser. No. US 2001-24046, filed on 21 Dec 2001, GRANTED, Pat. No. US 6706724

	NUMBER	DATE
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DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: EDWARD D GRIEFF, HALE & DORR LLP, 1455 PENNSYLVANIA AVE, NW, WASHINGTON, DC, 20004
NUMBER OF CLAIMS: 54
EXEMPLARY CLAIM: 1
LINE COUNT: 4760
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention describes novel substituted aryl compounds that are cyclooxygenase 2 (COX-2) selective inhibitors and novel compositions comprising at least one cyclooxygenase 2 (COX-2) selective inhibitor, and, optionally, at least one compound that donates, transfers or releases nitric oxide, stimulates endogenous synthesis of nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor or is a substrate for nitric oxide synthase, and/or, optionally, at least one therapeutic agent, such as, steroids, nonsterodal antiinflammatory compounds (NSAID), 5-lipoxygenase (5-LO) inhibitors, leukotriene B.sub.4 (LTB.sub.4) receptor antagonists, leukotriene A.sub.4 (LTA.sub.4) hydrolase inhibitors, 5-HT agonists, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) inhibitors, H.sub.2 antagonists, antineoplastic agents, antiplatelet agents, thrombin inhibitors, thromboxane inhibitors, decongestants, diuretics, sedating or non-sedating anti-histamines, inducible nitric oxide synthase inhibitors, opioids, analgesics, Helicobacter pylori inhibitors, proton pump inhibitors, isoprostane inhibitors, and mixtures thereof.. The invention also provides novel kits comprising at least one COX-2 selective inhibitor, and, optionally,

at least one nitric oxide donor, and/or, optionally, at least one therapeutic agent. The novel cyclooxygenase 2 selective inhibitors of the invention can be optionally nitrosated and/or nitrosylated. The invention also provides methods for treating inflammation, pain and fever; for treating and/or improving the gastrointestinal properties of COX-2 selective inhibitors; for facilitating wound healing; for treating and/or preventing renal toxicity or other toxicities; for treating and/or preventing other disorders resulting from elevated levels of cyclooxygenase-2; and for improving the cardiovascular profile of COX-2 selective inhibitors.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM [0520] Suitable proton pump inhibitors, include, but are not limited to, omeprazole, **esomeprazole**, lansoprazole, rabeprazole, pantoprazole, and the like. Suitable proton pump inhibitors are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995, Pgs. 901-915; the Merck Index on CD-ROM, Twelfth Edition, Version 12:1, 1996; and in WO 00/50037 assigned to NitroMed Inc., the disclosures of which are incorporated herein by reference in their entirety.

DETD [0683] To acetic anhydride (0.460 mL) at 0° C. was added drop-wise, with stirring, fuming nitric acid (0.140 mL). This mixture was immediately added drop-wise to a solution of the product of Example 18b (0.43 mmol, 0.216 g) dissolved in ethyl acetate (5 mL), at 0° C. The resulting solution was stirred at 0° C. for 30 min, then quenched with water and neutralized with sodium carbonate. The organic layer was separated, dried over magnesium sulfate and filtered. The filtrate was evaporated under reduced pressure. Purification by silica gel column chromatography using ethyl acetate as the eluant gave the title compound as an **amorphous** glassy solid (0.217 g, 92% yield). .sup.1H NMR (300 MHz, CDCl.sub.3) δ7.95 (d, J=8.0 Hz, 2H), 7.39 (d, J=8.0 Hz, 2H), 6.88 (m, 3H), 6.61 (t, J=8.8 Hz, 1H), 6.43 (m, 2H), 4.79 (m, 1H), 4.61 (m, 3H), 4.28 (dd, J=7.3, 11.4 Hz, 1H), 3.83 (s, 2H), 3.12 (s, 3H); MS (APIMS) m/e 503 (M+H-NO2).sup.+, 566 (M+18).sup.+.

DETD [0687] To acetic anhydride (0.230 mL) at 0° C. was added drop-wise, with stirring, fuming nitric acid (0.07 mL). This mixture was immediately added drop-wise to a solution of the product of Example 19a (0.25 mmol, 0.112 g) dissolved in ethyl acetate, at 0° C. The resulting solution was stirred at 0° C. for 15 min, then quenched with water and neutralized with sodium carbonate. The organic layer was separated, dried over magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure. Purification by silica gel column chromatography using ethyl acetate as the eluant gave the title compound as an **amorphous** glassy solid, (69 mg, 56% yield). .sup.1H NMR (300 MHz, CDCl.sub.3) δ7.91 (d, J=8.3 Hz, 2H), 7.35 (d, J=8.3 Hz, 2H), 6.81 (s, 0.5H), 6.80 (s, 0.5H), 6.79 (s, 0.5H), 6.78 (s, 0.5H), 6.59 (tt, J=2.3, 9.0 Hz, 1H), 6.41 (m, 2H), 4.73 (m, 2H), 4.57 (m, 1H), 4.35 (m, 1H), 4.18 (dd, J=3.2, 6.2 Hz, 0.5H), 4.14 (dd, J=3.2, 6.2 Hz, 0.5H), 3.79 (s, 2H), 3.09 (s, 3H); MS (APIMS) m/e 509 (M+18).sup.+.

L2 ANSWER 13 OF 42 USPATFULL on STN

ACCESSION NUMBER: 2004:151066 USPATFULL

TITLE: Hydrophobic active agent compositions and methods

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Venkateshwaran, Srinivasan, Salt Lake City, UT, UNITED STATES
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PATENT ASSIGNEE(S): Lipocine, Inc. (U.S. corporation)

amosulalol, amotriphene, amoxapine, amoxicillin, amphecloral, amphetamine, amphomycin, amphotericin, ampicillin, ampiroxicam, amprenavir, amrinone, amsacrine, amyl nitrate, amylobarbitone, anagestone acetate, anastrozole, andinocillin, androstenediol, androstenediol-17-acetate, androstenediol-17-benzoate, androstenediol-3-acetate, androstenediol-3-acetate-17-benzoate, androstenedione, androsterone acetate, androsterone benzoate, androsterone propionate, androsterone, angiotensin, anidulafungin, aniracetam, apazone, apicycline, apoatropine, apomorphine, apraclonidine, aprepitant, aprotinin, arbaprostil, ardeparin, aripiprazole, arnikacin, arotinolol, arstiinol, arylacetic acid derivatives, arylalkylamines, arylbutyric acid derivatives, arylcarboxylic acids, arylpiperazines, arylpropionic acid derivatives, aspirin, astemizole, atenolol, atomoxetine, atorvastatin, atovaquone, atropine, auranofin, azapropazone, azathioprine, azelastine, azetazolamide, azithromycin, baclofen, bambuterol, bamethan, barbitone, barnidipine, basalazide, beclamide, beclobrate, beclomethasone, befimolol, bemegride, benazepril, bencyclane, bendazac, bendazol, bendroflumethiazide, benethamine penicillin, benexate hydrochloride, benfurodil hemisuccinate, benidipine, benorylate, bentazepam, benzhexol, benziodarone, benznidazole, benzoctamine, benzodiazepine derivatives, benzodiazepine, benzonatate, benzphetamine, benzylmorphine, beperiden, bephenium hydroxynaphthoate, bepridil, bepridil, betahistine, betamethasone, betaxolol, bevantolol, bevonium methyl sulfate, bexarotene, bezafibrate, bialamicol, biapenem, bicalutamide, bietamiverine, bifonazole, binedaline, binifibrate, biricodar, bisacodyl, bisantrene, bisoprolol, bitolterol, bopindolol, boswellic acid, bradykinin, bretylium, bromazepam, bromocriptine, bromperidol, brotizolam, brovincamine, buciclate, bucloxic acid, bucumolol, budesonide, budralazine, bufeniode, bufetolol, buflomedil, bufuralol, bumetanide, bunitrolol, bupranolol, buprenorphine, buproprion, buspirone, busulfan, butalamine, butarphenol, butaverine, butenafine, butenafine, butidrine hydrochloride, butobarbitone, butoconazole nitrate, butoconazole, butofilol, butorphenol, butropium bromide, cabergoline, calcifediol, calcipotriene, calcitriol, caldiribine, cambendazole, camioxirole, camostat, camptothecin, candesartan, candoxatril, capecitabine, caprate, capsaicin, captopril, carazolol, carbacephems, carbamates, carbamezepine, carbapenems, carbarsone, carbatrol, carbenoxolone, carbimazole, carbromal, carbuterol, carisoprodol, carotenes, caroverine, carteolol, carvedilol, cefaclor, cefazolin, cefbuperazone, cefepime, cefoselis, ceftibuten, celcoxib, celecoxib, celiprolol, cephaeline, cephalosporin C, cephalosporins, cephamycins, cerivastatin, certoparin, cetamolol, cetiedil, cetirizine, cetraxate, chloracizine, chlorambucil, chlorbetamide, chlordantoin, chliordiazepoxide, chlormadinone acetate, chlormethiazole, chloroquine, chlorothiazide, chlorpheniramine, chlorphenoxamide, chlorphentermine, chlorproguanil, chlorpromazine, chlorpropamide, chlorprothixene, chlortetracycline, chlorthalidone, cholecalciferol, chromonar, ciclesonide, ciclonicate, cidofivir, ciglitazone, cilansetron, cilostazol, cimetidine, cimetropium bromide, cinepazet maleate, cinnamedrine, cinnarizine, cinolazepam, cinoxacin, ciprofibrate, ciprofloxacin, cisapride, cisplatin, citalopram, citicoline, clarithromycin, clebopride, clemastine, clenbuterol, clidanac, clinofibrate, clioquinol, clobazam, clobenfurol, clobenzorex, clofazimine, clofibrate, clofibric acid, cloforex, clomipramine, clonazepam, clonidine, clonitrate, clopidogrel, clopirac indomethacin, cloranolol, cloricromen, clorprenaline, clortermine, clotiazepam, clotrimazole, cloxacillin, clozapine, cmepazide, codeine methyl bromide, codeine phosphate, codeine sulfate, codeine, colloidal bismuth subcitrate, Complete List, cortisone, cromafiban, cromolyn, cropropamide, crotethamide, curcumin, cyclandelate, cyclarbamate, cyclazocine, cyclexedrine, cyclizine, cyclobenzaprine, cyclodrine,

cyclonium iodide, cyclopentamine, cyclosporine, cypionate, cyproheptadine, cyproterone acetate, cyproterone, cytarabine, dacarbazine, dalfopristine, dantrolene sodium, dapiprazole, darodipine, decanoate, decitabine, decoquinate, dehydroemetine, dehydroepiandrosterone, delavirdine, delaviridine, demeclocycline, denopamine, deramciclone, descitalopram, desipramine, desloratadine, desogestrel, desomorphine, desoxymethasone, detomidine, dexamethasone, dexamphetamine, dexanabinol, dexchlorpheniramine, dexfenfluramine, dexmethylphenidate, dexrazoxane, dextroamphetamine sulfate, dextroamphetamine, dextropropoxyphene, DHEA, diacetate, diamorphine, diazemine, diazepam, diazoxide, dibromopropamidine, dichlorophen, diclofenac, dicoumarol, didanosine, dideoxyadenosine, diethylpropion, difemerine, difenamizole, diflunisal, digitoxin, digoxin, dihidroergotamine, dihydrocodeine, dihydrocodeinone enol acetate, dihydroergotamine mesylate, dihydroergotamine, dihydrogesterone, dihydromorphine, dihydropyridine derivatives, dihydrostreptomycin, dihydrotachysterol, dihydroxyaluminum acetylsalicylate, diiodohydroxyquinoline, diisopromine, dilazep, dilevalol, dilitazem, diloxanide furoate, diloxanide, diltiazem, dimefline, dimenhydrinate, dimethisterone, dimetofrine, dimorpholamine, dinitolmide, dioxaphetyl butyrate, dioxethedrine, dipheniethoxidine, diphenhydramine, diphenoxylate, diphetarsone, dipivefrin, diponium bromide, dipyridamole, dirithromycin, disopyramide, divalproex sodium, dofetilide, domperidone, donezepil, dopexamine, dopradil, dosmalfate, doxapram, doxazosin, doxefazepam, doxepin, doxycycline, drofenine, dromostanolone propionate, dromostanolone, dronabinol, droperidol, droprenilamine, d-threo-methylphenidate, duloxetine, dutasteride, ebrotidine, eburnamonine, ecabet, ecenofloxacin, econazole nitrate, edavarone, edoxudine, efavirenz, effivarenz, efloxate, eledoisin, eletriptan, elgodipine, ellipticine, emepronium bromide, emetine, enalapril, enanthate, encainide, enlopitat, enoximone, enprostil, entacapone, epanolol, ephedrine, epinastine, epinephrine, epirubicin, epleronone, eposartan, ergocalciferol, ergoloid mesylates, ergotamine, ertapenum, erythromycin, erytlirityl tetranitrate, esaprazole, escitalopram, esmolol, **esomeprazole**, esonarimod, estazolam, estradiol benzoate, estradiol, estramustine, estriol succinate, estriol, estrone acetate, estrone sulfate, etafedrine, etafenone, ethacrynic acid, ethamivan, ethinamate, ethinylestradiol 3-acetate, ethinylestradiol 3-benzoate, ethinylestradiol, ethionamide, ethisterone (17α-ethinyltestosterone), ethopropazine, ethotoin, ethoxyphenamine, ethylestrenol, ethylmorphine, ethylnorepinephrine, ethynodiol diacetate, etodolac, etofibrate, etoposide, etoricoxib, etretinate, everolimus, exalamide, examestane, examorelin, ezemitibe, falecalcitriol, famciclovir, famotidine, fantofarone, farapenum, farglitazar, fasudil, felbamate, felodipine, fenalamide, fenbufen, fenbutrazate, fendiline, fenfluramine, fenofibrate, fenofibric acid, fenoldopam, fenoprofen, fenoterol, fenoverine, fenoxazoline, fenoxedil, fenpiprane, fenproporex, fenspiride, fentanyl, fexofenadine, flavoxate, flecainide, flopropione, floredil, floxuridine, fluconazole, flucytosine, fludarabine, fludiazepam, fludrocortisone, flufenamic acid, flunanisone, flunarizine, flunisolide, flunitrazepam, fluocortolone, fluoxetine, flupenthixol decanoate, fluphenazine decanoate, fluphenazine enanthate, fluphenazine, fluproquazone, flurazepam, flurbiprofen, flurogestone acetate, fluticasone propionate, fluvastatin, fluvoxamine, fominoben, formoterol, foscarnet, foscarnet, fosinopril, fosphenyloin, frovatirptan, fudosteine, fumagillin, furazolidone, furazolidone, furfurylmethyl amphetamine, furosemide, gabapentin, gabexate, gaboxadol, galanthamine, gallopamil, gammaparin, ganciclovir, ganglefene, gefarnate, gemcitabine, gemfibrozil, gepirone, gestadene, ghrelin, glatiramer, glaucarubin, glibenclamide, gliclazide, glimepiride, glipizide, gluconic acid, glutamicacid, glyburide, glyceryl trinitrate, glymepiride, granisetron, grepafloxacin, griseofulvin, guaiazulene,

guanabenz, guanfacine, halofantrine, haloperidol decanoate, haloperidol, haloxazolam, hepronicate, heptanoate, hexobendine, hexoprenaline, hydramitrazine, hydrazides, hydrochlorothiazide, hydrocodone, hydrocortisone, hydromorphone, hydroxyamphetamine, hydroxymethylprogesterone acetate, hydroxymethylprogesterone, hydroxyprogesterone acetate, hydroxyprogesterone caproate, hydroxyprogesterone, hymecromone, hyoscyamine, ibopamine, ibudilast, ibufenac, ibuprofen, ibutilide, idebenone, idoxuridine, ifenprodil, igmesine, iloprost, imatinib, imidapril, imidazoles, imipenem, imipramine, imolamine, incadronic acid pergolide, indanazoline, indenolol, indinavir, indomethacin, indoramin, inosinepranobex, inositol niacinate, iodoquinol, ipidracine, iproniazid, irbesartan, irinotecan, irsogladine, isobutyrate, isocaprate esters, isoetharine, isometheptene, isoproterenol, isosorbide dinitrate, isosorbide mononitrate, isosorbide dinitrate, isoxsuprine, isradipine, itasetron, itraconazole, itramintosylate, ivermectin, kallidin, kallikrein, kanamycin, ketamine, ketoconazole, ketoprofen, ketorolac, ketotifen, labetalol, lafutidine, lamifiban, lamivudine, lamotrigine, lanatoside c, lansoprazole, lasofoxifene, leflunomide, leminoprazole, lercanadipine, lesopitron, letrozole, leucovorin, levalbuterol, levallorphan, levetiracetam, levetriacetam, levobunolol, levodopa, levofloxacin, levonorgestrel, levophacetoperane, levorphanol, lidocaine, lidoflazine, lifibrol, limaprost, linezolid, lintitript, liranaftate, lisinopril, lisuride, lobeline, lobucavir, lodoxamide, lomefloxacin, lomerizine, lomustine, loperamide, lopinavir, loprazolam, loracarbef, loratadine, lorazepam, lorefloxacin, lormetazepam, losartan, lovasatain, lovastatin, loxapine succinate, loxapine, 1-threo-methylphenidate, lumiracoxib, lynestrenol, lysine acetylsalicylate, lysozyme, lysuride, mabuterol, mafenide, magnesium acetylsalicylate, malgramostin, mannitol hexanitrate, maprotiline, mazindol, mebendazole, meclizine, meclofenamic acid, mecloxaminepentapiperide, medazepam, medibazine, medigoxin, medrogestone, medroxyprogesterone acetate, mefenamic acid, mefenorex, mefloquin, mefloquine, megestrol acetate, megestrol, melengestrol acetate, melphalan, mematine, mepenzolate bromide, meperidine, mephenoxalone, mephentermine, mepindolol, mepixanox, meprobamate, meptazinol, mercaptopurine, merropenum, mesalamine, mesalazine, mesoridazine, besylate, mesoridazine, mestranol, metaclazepam, metamfepramone, metampicillin, metaproterenol, metaraminol, methacycline, methadone hydrochloride, methadone, methamphetamine, methaqualone, methamphetamine, methoin, methotrexate, methoxamine, methsuximide, methylhexaneamine, methylphenidate d-threo-methylphenidate, methylplienidate, methylphenobarbitone, methylprednisolone, methysergide, metiazinic acid, metizoline, metoclopramide, metolazone, metoprolol, metoxalone, metripranolol, metronidazole, mexiletine, mexilitene, mianserin, mibefradil, miconazole, midazolam, midodrine, miglitol, milnacipran, milrinone, minoxidil, mirtazapine, misoprostol, mitomycin, mitotane, mitoxantrone, mizolastine, modafinil, mofebutazone, mofetil, molindone hydrochloride, molindone, molsidomine, monatepil, montelukast, monteplase, moprolol, moricizine, morphine hydrochloride, morphine sulfate, morphine, morpholine salicylate, mosapramine, moxifloxacin, moxisylvyte, moxonidine, mycophenolate, nabumetone, nadolol, nadoxolol, nadroparin, nafamostat, nafronyl, naftopidil, nalbuphine, nalidixic acid, nalmefene, nalorphine, naloxone, naltrexone, nandrolone benzoate, nandrolone cyclohexanecarboxylate, nandrolone cyclohexane-propionate, nandrolone decanoate, nandrolone furylpropionate, nandrolone phenpropionate, naphazoline, naproxen, naratriptan, natamycin, nateglinide, nebivalol, nedocromil, nefazodone, nefopam, nelfinavir, nemonapride, neomycin undecylenate, neomycin, neotrofin, nesiritide, n-ethylamphetamine, nevibulol, nevirapine, nexopamil, nicametate, nicardipine, nicergoline, nicofibrate, nicofuranose, nicomorphine, nicorandil, nicotinyl alcohol, nicoumalone, nifedipine, nifenalol, nikethamide, nilutamide,

nilvadipine, nimodipine, nimorazole, nipradilol, nisoldipine, nitisonone, nitrazepam, nitrofurantoin, nitrofurazone, nitroglycerin, nizatidine, norastemizole, norepinephrine, norethindrone acetate, norethindrone, norethisterone acetate, norethisterone, norethynodrel, norfenefrine, norfloxacin, norgestimate, norgestrel, norgestrienone, normethadone, normethisterone, normorphine, norpseudoephedrine, nortriptyline, novantrone, nylidrin, nystatin, octamylamine, octodrine, octopamine, ofloxacin, olanzapine, olanzapine, olapatadine, olmesartan, olopatidine, olsalazine, omapatrilat, omeprazole, ondasetron, opium, oprevelkin, orlistat, ornidazole, ornoprostil, oseltamivir, oxaliplatin, oxamniquine, oxandrolone, oxantel embonate, oxaprozin, oxatomide pemirolast, oxatomide, oxazepam, oxcarbazepine, oxfendazole, oxiconazole, oxiracetam, oxolinicacid, oxprenolol, oxycodone, oxyfedrine, oxymetazoline, oxymorphone, oxyphenbutazone, oxyphencyclimine, oxyprenolol, ozagrel, paclitaxel, palonosetron, pantoprazole, papaverine, paracalcitol, paramethadione, parecoxib, pariprazole, paromomycin, paroxetine, parsalmide, pazinaclone, pemoline, penbutolol, penciclovir, penicillin G benzathine, penicillin G procaine, penicillin V, penicillins, pentaerythritol tetranitrate, pentaerythritol tetranitrate, pentapiperide, pentazocine, pentifylline, pentigetide, pentobarbitone, pentorex, pentoxifylline, pentrinitrol, perbuterol, perenzepine, pergolide, perhexiline, perindopril erbumine, perospirone, perphenazine pimozide, perphenazine, phanquinone, phenacemide, phenacetin, phenazopyridine, phencarbamide, phendimetrazine, phenelzine, phenindione, phenmetrazine, phenobarbitone, phenoperidine, phenothiazines, phenoxybenzamine, phensuximide, phentermine, phentolamine, phenyl salicylate, phenylacetate, phenylbutazone, phenylephrinehydrochloride, phenylpropanolamine hydrochloride, phenylpropanolaminehydrochloride, phenylpropyl-methylamine, phenyloin, phloroglucinol, pholedrine, physostigmine salicylate, physostigmine, phytonadiol, piapenum, picilorex, piclamilast, picrotoxin, picumast, pifamine, pilsicainide, pimagedine, pimeclone, pimecrolimus, pimethylline, pimozide, pinaverium bromide, pindolol, pioglitazone, piperacillin, piperazine estrone sulfate, piperazine derivatives, piperilate, piracetam, pirbuterol, pirenzepine, piribedil, pirifibrate, piroxicam, pitavastatin, pizotyline, plaunotol, polaprezinc, polybenzarsol, polyestrol phosphate, practolol, pralnacasan, pramipexole, pranlukast, prasterone, pravastatin, prazepam, praziquantel, prazosin, prednisolone, prednisone, pregabalin, prenalterol, prenylamine, pridinol, prifinium bromide, primidone, primipramine, probenecid, probucol, procainamide, procarbazine, procaterol, prochlorperazine, progesterone, proguanil, pronethalol, propafenone, propamidine, propatyl nitrate, propentoffyline, propionate, propiram, propoxyphene, propranolol, propylhexedrine, propylthiouracil, protokylol, protriptyline, proxazole, pseudoephedrine, purines, pyrantel embonate, pyrazoles, pyrazolones, pyridofylline, pyrimethamine, pyrimidines, pyrrolidones, quazepam, quetiapine, quetuapine, quinagolide, quinapril, quinestrol, quinfamide, quinidine, quinine sulfate, quinolones, quinupritin, rabalzotan, rabeprazole sodium, rabeprazole, racefimine, ramatroban, ramipril, ranitidine, ranolazine, ransoprazole, rasagiline, rebamipide, refludan, repaglinide, repinotan, repirinast, reproterol, reserpine, retinoids, ribavirin, rifabutine, rifampicin, rifapentine, rilmenidine, riluzole, rimantadine, rimiterol, rioprostil, risperidone, ritanovir, ritapentine, ritipenem, ritodrine, ritonavir, rivastigmine, rizatriptan, rociverine, rofecoxib, rohypnol, rolipram, romoxipride, ronifibrate, ropinirole, ropivacaine, rosaprostol, rosiglitazone, rosuvastatin, rotinolol, rotraxate, roxatidine acetate, roxindole, rubitecan, salacetamide, salicin, salicylamide, salicylic acid derivatives, salmeterol, saquinavir, saquinavir, scopolamine, secnidazole, selegiline, semotiadil, seratrodast, sertindole, sertraline, sibutramine, sildenafil, simfibrate, simvastatin, siramesine, sirolimus, sitaxsentan, sofalcone,

somotiadil, sorivudine, sotalol, soterenol, sparfloxacin, spasmolytol, spectinomycin, spiramycin, spironolactone, spizofurone, stanozolol, stavudine, streptomycin, succinylsulfathiazole, sucralfate, sufentanil, sulconazole nitrate, sulfacetamide, sulfadiazine, sulfaloxicacid, sulfarside, sulfinalol, sulindac, suloctidil, sulphabenzamide, sulphacetamide, sulphadiazine, sulphadoxine, sulphafurazole, sulphamerazine, sulphamethoxazole, sulphapyridine, sulphasalazine, sulphinpyrazone, sulpiride, sulthiame, sultopride, sultroponium, sumanirole, sumatriptan, sunepitron, superoxide dismutase, suplatast, suramin sodium, synephrine, tacrine, tacrolimus, tacrolimus, tadalafil, talinolol, talipexole, tamoxifen, tamsulosin, targretin, tazanolast, tazarotene, tazobactum, tecastimezole, teclozan, tedisamil, tegaserod, telenzepine, telmisartan, temazepam, teniposide, teprenone, terazosin, terbenafine, terbinafine, terbutaline sulfate, terbutaline, terconazole, terfenadine, terodiline, terofenamate, tertatolol, testolactone, testosterone, tetracyclics, tetracycline, tetrahydrocannabinol, tetrahydrozoline, thalidomide, theofibrate, thiabendazole, thiazinecarboxamides, thiocarbamates, thiocarbamizine, thiocarbarsone, thioridazine, thiothixene, tiagabine, tiamenidine, tianeptine, tiaprofenic acid, tiaramide, ticlopidine, tigloidine, tilisolol, timolol, tinidazole, tinofedrine, tinzaparin, tioconazole, tipranavir, tirapazamine, tirofiban, tiropramide, titanicene, tizanadine, tizanidine, tizinadine, tocainide, tolazamide, tolazoline, tolbutamide, tolcapone, tolciclate, tolfenamic acid, toliprolol, tolteridine, tolterodine, tonaberstat, topiramate, topotecan, torasemide, toremifene citrate, toremifene, tosufloxacin, tramadol, tramazoline, trandolapril, tranilast, tranylcypromine, trapidil, traxanox, trazodone, tretoquinol, triacetin, triamcinolonc, triampterine, triamterine, triazolam, triazoles, tricromyl, tricyclics, trifluoperazine hydrochloride, trifluoperazine, triflupromazine, trifluridine, trihexyphenidyl hydrochloride, trihexyphenidyl, trimazosin, trimebutine, trimetazidine, trimethoprim, trimgestone, trimipramine, trimoprostil, trithiozine, troglitazone, trolnitrate phosphate, tromethamine, tropicamide, trovafloxacin, troxipide, tuaminoheptane, tulobuterol, tymazoline, tyramine, undecanoate, undecanoic acid, urinastatin, ursodeoxycholic acid, valacyclovir, valdecoxib, valerate, valganciclovir, valproic acid, valsartan, vancomycin, vardenafil, venlafaxine, venorelbine, verapamil, verapimil, vidarabine, vigabatrin, vincamine, vinpocetine, viomycin, viquidil, visnadine, vitamin a derivatives, vitamin a, vitamin b2, vitamin d, vitamin e, vitamin k, voglibose, voriconazole, xaliproden, xamoterol, xanthinol niacinate, xenytropium bromide, xibenolol, ximelagatran, xylometazoline, yohimbine, zacopride, zalirlukast, zafirlukat, zalcitabine, zaleplon, zanamivir, zatebradine, ziconotide, zidovudine, zileuton, zimeldine, zinc propionate, ziprasidone, zolimidine, zolmitriptan, zolpidem, zonisamide, zopiclone. The more preferred active agents include alendronate, amiodarone, amlodipine, amprenavir, anastrozole, aprepitant, aripiprazole, atomoxetine, atorvastatin, atovaquone, azathioprine, azelastine, azithromycin, bicalutamide, budesonide, buproprion, butarphenol, butorphenol, candesartan, carbamezepine, carisoprodol, carvedilol, celcoxib, cetirizine, ciclesonide, cilostazol, clopidogrel, cyclobenzaprine, delaviridine, deramciclone, descitalopram, desloratadine, DHEA, didanosine, dihidroergotamine, dipyridamole, donezepil, dronabinol, duloxetine, dutasteride, effivarenz, enlopitat, entacapone, epirubicin, ergotamine, etoricoxib, everolimus, ezemitibe, felodipine, fentanyl, frovatirptan, gabapentin, granisetron, halofantrine, hydrocodone, itasetron, lamotrigine, lansoprazole, leflunomide, lercanadipine, letrozole, letrozole, levetiracetam, lovasatain, lumiracoxib, malgramostin, mefloquin, mematine, mesalamine, metolazone, mirtazapine, modafinil, nefazodone, nelifinavir, nifedipine, nilutamide, nimodipine, nisoldipine, norastemizole, norfloxacin, olanzapine, olapatadine, ondasetron, oxaprozin, oxcarbazepine, oxycodone, perbuterol,

phenazopyridine, pimecrolimus, pioglitazone, pralnacasan, prasterone, pravastatin, propafenone, quetuapine, repaglinide, riluzole, risperidone, ritanovir, rivastigmine, rofecoxib, saquinavir, sertindole, sertraline, sildenafil, simvastatin, sirolimus, spironolactone, stavudine, sumatriptan, tacrolimus, tadalafil, tamsulosin, tazarotene, tazarotene, tecastimezole, tegaserod, terbenafine, thalidomide, tiagabine, tizanadine, tizinadine, tolcapone, tolteridine, topiramate, torasemide, toremifene, tramadol, valdecoxib, valproic acid, vardenafil, vigabatrin, voriconazole, ximelagatran, zafirlukat, zaleplon, zileuton, ziprasidone, zolpidem, zonisamide.

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ACCESSION NUMBER: 2004:101999 USPATFULL
TITLE: Process for preparation of optically pure or optically enriched sulfoxide compounds, including **amorphous esomeprazole** and salts thereof
INVENTOR(S): Reddy, Manne Satyanarayana, Ameerpet Hyderabad, INDIA
Kumar, Muppa Kishore, Ameerpet Hyderabad, INDIA
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Sreenath, Keshaboina, Ameerpet Hyderabad, INDIA
PATENT ASSIGNEE(S): DR. REDDY'S LABORATORIES LIMITED (non-U.S. corporation)
DR. REDDY'S LABORATORIES, INC. (non-U.S. corporation)

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LINE COUNT: 1071
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A process of preparation of optically pure or optically enriched isomers of omeprazole and structurally related sulfoxides is provided. Also provided are an **amorphous** form of **esomeprazole**, as well a pharmaceutical composition containing it and a method of using it for treatment of gastric disorders.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI Process for preparation of optically pure or optically enriched sulfoxide compounds, including **amorphous esomeprazole** and salts thereof
AB A process of preparation of optically pure or optically enriched isomers of omeprazole and structurally related sulfoxides is provided. Also provided are an **amorphous** form of **esomeprazole**, as well a pharmaceutical composition containing it and a method of using it for treatment of gastric disorders.
SUMM [0003] Omeprazole and structurally similar sulfoxide compounds are known inhibitors of gastric acid secretion and are used as anti-ulcer agents. The sulfur atom of the sulfoxide group in asymmetrically substituted sulfoxides is chiral. Therefore, omeprazole and related sulfoxides

exhibit optical isomerism at the sulfur atom of the sulfoxide. In fact, omeprazole exists as a pair of enantiomers; the S (-) enantiomer is referred to as **esomeprazole.**

SUMM [0019] In a more preferred embodiment, the invention provides a specific process for preparing a substantially enantiomerically pure or enantiomerically enriched form of omeprazole and its salts. In other preferred aspect, the invention also provides an **amorphous** form of **esomeprazole** and pharmaceutical compositions containing such **amorphous** form, as well as a related method of treatment.

DRWD [0020] FIG. 1 shows an X-Ray Powder Diffractogram of **amorphous esomeprazole.**

DETD [0045] The preferred embodiment of the process aspect of the invention involves preparation of the (S) enantiomer of omeprazole, known as **esomeprazole**, and its salts. The scheme illustrates the preferred process contemplated by the inventors: ##STR11##

DETD [0046] Thus, in accordance with the particular variant of the process aspect of the invention, the sodium salt of omeprazole (1) is suspended in acetone or another ketone solvent. The starting salt (2) may be purchased from a commercial source, if available. Alternatively, sodium salt of omeprazole (2) may be obtained by treating free species omeprazole with sodium hydroxide in a suitable solvent, preferably, alcohol, such as methanol or isopropanol. The suspension of racemic sodium salt of omeprazole is treated with titanium (IV) isopropoxide, diethyl D-tartrate in the presence of organic base. The preferred bases are diisopropyl ethylamine and triethylamine. Titanium isopropoxide is the coordinating agent and diethyl tartrate is the chelating agent. The resulting titanium complex (3) is then treated with L (+) mandelic acid to obtain mandelic acid salts (4A) and (4B). The salt (4A) is derived from enantiomer of omeprazole having S configuration at the sulfur atom of the sulfoxide. The salt (4B) is derived from enantiomer with R configuration. The salts (4A) and (4B) are related diastereomerically, and thus have different physical properties. The inventors have found that when diethyl D tartrate and L (+) mandelic acid are used in the process, the salt (4A) has lower solubility in ketone solvent, particularly acetone. The amount of solvent may be selected in such a manner that the less soluble salt (4A) substantially precipitates out while the more soluble salt (4B). Interestingly, the inventors also found that if enantiomer derived from R-configured isomer of omeprazole is more desired, diethyl L tartrate and D (-) mandelic acid may be used in the process, with salt derived from such R-configured isomer having lower solubility in ketone solvents. In the preferred variant, after addition of mandelic acid, the reaction mixture is maintained with stirring from at least about 15 minutes and up to about 5 hours at ambient temperature. The salt (4A) precipitates while the salt (4B) remains in solution. The separated solid salt (4A) is filtered and suspended in a mixture of aqueous base and chlorinated solvent. The preferred aqueous base is a diluted solution of sodium bicarbonate. The preferred chlorinated solvents include chloroform, dichloromethane, and carbon tetrachloride. In the basic conditions, the salt (4A) is converted to S-enantiomer of omeprazole (5A). The organic layer of the bi-phasic reaction mixture, which contains the free species of **esomeprazole**, is separated. The compound (5A) (**esomeprazole**, free species) may be isolated in any manner known to those of skill in the art.

DETD [0047] In one variant, the organic solvent is removed, for example by vacuum distillation, and the residue of the compound (5A) is re-precipitated from a mixture of water and ketone solvent, preferably acetone. In a non-limiting example, **esomeprazole** residue is combined with water/acetone mixture (about 1:2 by volume) and stirred to

dissolve the residue. The solution is cooled to 5-10° C., and maintain at that temperature until solid mass of **esomeprazole** separates. The mass is filtered and dried at 25-30° C. to a constant weight. The solid **esomeprazole** produced in this manner may then be dried, preferably under reduced pressure, and more referably under rotation (for example, in a Buchi rotavapor flask at about 750 mm/Hg) at a temperature of about 25° C. to about 30° C. This drying method is believed to provide a non-solvated, free-flowing solid. **Esomeprazole** solid obtained in such manner was found to be **amorphous**. FIG. 1 shows an X-ray diffractogram of this **esomeprazole** solid. The X-ray powder diffraction pattern of FIG. 1 was measured on a Bruker Axs, D8 advance Powder X-ray diffractometer with Cu K alpha-I radiation source. No significant peaks are observable, which is characteristic of an **amorphous** material. Thus, in another preferred aspect, the invention also provides **amorphous esomeprazole**. If desired, the **amorphous esomeprazole** may then be converted into pharmaceutically-acceptable salts, such as magnesium, sodium, or potassium and their hydrates.

DETD [0048] In another variant, the free species compound (5A) may be converted to a salt (6A). For example, the solvent may be removed and the residue of the compound (5A) may be treated with an alkali base in a manner known to those skilled in the art. Also, the residue may be treated with a free earth alkaline metal, preferably, in alcoholic solvent to obtain a desired salt of the metal. In a non-limiting example, magnesium salt of **esomeprazole**, believed to be in a trihydrate form, may be obtained as follows. A magnesium metal is suspended in methanol in the presence of dichloromethane; the mass is cooled to 5-10° C., and compound (5A) is added. After salt formation is complete, the reaction mixture is mixed with large quantity of water and the mixture is stirred until the solid mass of the magnesium salt of **esomeprazole** (compound (6A) when M is magnesium) separates from the liquid phase. The solid mass is filtered, re-dissolved in methanol and filtered again to remove un-reacted magnesium metal. The solvent is removed and the residue is crystallized from acetone at 5-10° C. to afford magnesium salt of **esomeprazole** trihydrate.

DETD [0050] The process as described, or portions thereof, may be repeated to improve the optical purity of the product sulfoxides. The process may be used to produce sulfoxide products, such as the magnesium trihydrate salt of the S enantiomer of omeprazole, at an optical purity and in enantiomeric excess greater than about 97%, preferably, greater than about 98%, more preferably, greater than about 98.5%, and, yet more preferably, greater than about 99%. As noted earlier, the nature of the reagents may be used to vary the principal product of the process. For example, in a particular variant, to obtain **esomeprazole**, diethyl-D-tartrate and L mandelic acid are preferably used; while diethyl L tartrate and D mandelic acid are used to obtain the R enantiomer of omeprazole. Examples of single or enriched enantiomeric sulfoxides salts and hydrates that may be synthesized by the process of the invention are the R (-) enatiomer of omeprazole, its pharmaceutically acceptable salt and their hydrates, the S (+) enatiomer of omeprazole, its salt and their hydrates, the magnesium salt of the S (+) enantiomer of omeprazole and its hydrate, the sodium salt of the S (+) enantiomer of omeprazole and its hydrate, the potassium salt of the S (+) enantiomer of omeprazole and its hydrate, the magnesium salt of the R (-) enantiomer of omeprazole, the sodium salt of the R (-) enantiomer of omeprazole and its hydrate, the potassium salt of the R (-) enantiomer of omeprazole and its hydrate, and the magnesium trihydrate salt of the R (-) enantiomer of omeprazole, among many others.

DETD [0051] Pharmaceutical compositions that include one or more compounds

obtained by the process aspect of the invention are also provided. In particular, in one variant, a pharmaceutical composition that includes the **amorphous esomeprazole** produced as described above is also provided. In addition to the active compound, the pharmaceutical composition includes one or more pharmaceutically acceptable excipients, which ordinarily lack pharmaceutical activity, but have various useful properties which may, for example, enhance the stability, sterility, bioavailability, and ease of formulation of a pharmaceutical composition. The excipients may be solid, semisolid, or liquid, and may be formulated with the compound in bulk, but ultimately in the form of a unit-dose formulation (i.e., a physically discrete unit containing a specific amount of active ingredient) such as a tablet or capsule. The pharmaceutical composition of this aspect of the invention may include, in addition to a compound of this invention, one or more active pharmaceutical compounds.

DETD [0053] The more preferred oral solid preparation is a tablet. A tablet may be prepared by direct compression, wet granulation, or molding, of the **amorphous** form of **esomeprazole** with a carrier and other excipients in a manner known to those skilled in the art. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active agent or dispersing agent. Molded tablets may be made on a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent are suitable in the case of oral solid dosage forms (e.g., powders, capsules, and tablets). If desired, tablets may be coated by standard techniques. The **amorphous** form of **esomeprazole** described herein may be formulated into typical disintegrating tablet, or into a controlled or extended release dosage forms. Examples of suitable controlled release formulation vehicles are disclosed in U.S. Pat. Nos. 3,845,770; 3,916,899; 3,536,809; 3,598,123; and 4,008,719, the disclosures of which are hereby incorporated by reference in their entirety.

DETD Preparation of Mandelic Acid Titanium Complex Salt of **Esomeprazole**

DETD [0069] Mandelic acid titanium complex salt of **Esomeprazole** obtained as described in Example 1 (75.0 grams) was suspended in a mixture of dichloromethane (375 ml), and 5% sodium bicarbonate solution (375 ml), further stirred for 15-30 minutes. The dichloromethane layer was separated from the resulting solution, and the solvent was distilled off completely to get the title compound as a residual mass. The characteristics of the thus resulting product were as follows. Weight: 37.0 g. Chiral Purity: 99.85%.

DETD [0070] Magnesium metal (1.33 grams) and Dichloromethane (3.7 ml) were added to methanol (111 ml) and stirred for 1-2 hours. The mass was cooled to a temperature of 5-10° C., **esomeprazole** obtained in Example 2 (37.0 grams) and methanol (111.0 ml) were added accompanied by stirring for 15-30 minutes. The reaction mass was decomposed into water (666 ml) at a temperature of 5-10° C. over a period of 45-60 minutes, and then further stirred for 30-45 minutes to separate the solid mass. The solid mass was filtered, and washed with water (222 ml). The thus obtained compound was dissolved in methanol (222 ml), and filtered off the solution to separate any excess magnesium. The solvent was removed from the filtrate to get the residual mass. The residual mass was crystallized in Acetone (278 ml) at a temperature of 0-5° C. to afford optically pure **Esomeprazole** magnesium trihydrate salt. The resulting product had the following characteristics. Weight: 11.5 g. Chiral Purity: .about.100%. Optical rotation: -125° (c=0.5% methanol)

DETD [0072] Sodium hydroxide flakes (4.5 grams) were added to methanol (50 ml) and stirred for 15-30 minutes. The mass was cooled to a temperature of 5-10° C., **esomeprazole** obtained as in Example 2

(25.0 grams), and methanol (100.0 ml) were added with stirring for 30-60 minutes. The solvent was expelled off completely from the reaction solution. Di-isopropyl ether (150 ml) was added to the residual mass and further stirred for 30-60 minutes. The mass was cooled to a temperature of 0-5° C. and stirred for 30-60 minutes to separate the solid mass. The solid mass was filtered and dried at a temperature of 60-70° C. under vacuum to afford optically pure **Esomeprazole** Sodium trihydrate salt. The characteristics of the product are as follows. Weight: 14.5 g. Chiral Purity: 99.53 Optical rotation: +42° (c=0.5% water)

DETD [0074] Potassium hydroxide flakes (6.3 grams) were added to methanol (50 ml) and stirred for 15-30 minutes. The mass was cooled to a temperature of 5-10° C., **esomeprazole** obtained by the method of Example 2 (25.0 grams) and methanol (100.0 ml) were added accompanied by stirring for 30-60 minutes. The solvent was expelled off completely from the reaction solution. Di-isopropyl ether (150 ml) was added to the residual mass and further stirred for 30-60 minutes. The mass was cooled to a temperature of 0-5° C. and stirred for 30-60 minutes to separate the solid mass. The solid mass was filtered and dried at a temperature of 60-70° C. under vacuum to afford optically pure **Esomeprazole** Sodium trihydrate salt. The characteristics of the product were as follows: Weight: 12.0 grams, Chiral Purity: 100%, Optical rotation: +28.00 (c=1% water). The sodium dihydrate salt of the S (-) enantiomer of Omeprazole was prepared in the same manner shown above by a controlled drying process.

DETD [0075] **Esomeprazole** (20.0 grams, obtained as per Example-2) was dissolved in a mixture of acetone (100 ml) and water (200 ml), and stirred for 15-30 minutes. The pH of the mass was adjusted with caustic lye to 12 to 13 accompanied by stirring for 30-60 minutes. The reaction solution was subjected to carbon treatment at atmospheric temperature. The pH was further adjusted to 7 to 8 with acetic acid, and the reaction mass cooled to a temperature of 5-10° C. and stirred for 1-2 hours to crystallize the solid mass. The solid mass was filtered, washed with water (100 ml), and dried under vacuum at a temperature of 25-30° C. to a constant weight. The characteristics of the thus obtained product were. Weight: 7.0 g. Chiral Purity: 99.94%

CLM What is claimed is:

46. The process of claim 45, further comprising reacting said mandelic acid salt with an aqueous base thereby obtaining a residue, which is a free species of **esomeprazole.**

47. The process of claim 45, further comprising re-precipitating said residue from a mixture of water and acetone to obtain a solid that is an **amorphous** form of free species of **esomeprazole.**

48. The process of claim 45, further comprising reacting said free species of omeprazole with a magnesium metal in the presence of dichloromethane in an alcoholic solvent thereby obtaining a residue of magnesium salt of **esomeprazole.**

49. A magnesium salt of **esomeprazole** produced by the process of claim 48.

50. The process of claim 48, further comprising dissolving said residue of magnesium salt of **esomeprazole** in acetone and lowering the temperature of said acetone solution to cause the magnesium salt of **esomeprazole** to precipitate therefrom.

51. A magnesium salt of **esomeprazole** produced by the process of claim 50.

57. A compound which the **amorphous esomeprazole**

produced by the process of claim 47.

58. A pharmaceutical composition comprising i) the **amorphous esomeprazole** produced by the process of claim 47; and ii) one or more pharmaceutically-acceptable excipients.

61. A method of preventing or treating undesirable gastric acid secretion or stomach ulcers, comprising administering to a subject in need thereof a pharmaceutical composition containing an effective amount of the **amorphous esomeprazole** produced by the process of claim 47.

L2 ANSWER 15 OF 42 USPATFULL on STN

ACCESSION NUMBER:	2004:63383 USPATFULL			
TITLE:	Absorbing agents and cover layer which is impermeable to active substances and which contains channel-formers or removable protective layer of a transdermal therapeutic system			
INVENTOR(S):	Beier, Cornelia, Holzkirchen, GERMANY, FEDERAL REPUBLIC OF Kibele, Ralf, Holzkirchen, GERMANY, FEDERAL REPUBLIC OF			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2004047901	A1	20040311	
APPLICATION INFO.:	US 2003-433373	A1	20030911	(10)
	WO 2001-EP14280		20011205	
	NUMBER		DATE	
PRIORITY INFORMATION:	DE 2000-10060852		20001206	
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	APPLICATION			
LEGAL REPRESENTATIVE:	Ronald R Santucci, Frommer Lawrence & Haug, 745 Fifth Avenue, New York, NY, 10151			
NUMBER OF CLAIMS:	27			
EXEMPLARY CLAIM:	1			
NUMBER OF DRAWINGS:	11 Drawing Page(s)			
LINE COUNT:	990			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This present invention concerns a cover layer that is impermeable to the active substances and/or a removable protective layer of a transdermal therapeutic system, comprising a thermoplastic film which either directly contains the absorbing agents and channel-forming agents or is coated with a polymer support (thermoplast) containing these substances. The polymer support can either be applied over the entire surface of the film or in patterns, directly during production. The thermoplastic film that is used and the polymer support can be made from either the same or different materials.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM [0024] As other potential absorbing agents, metals and alloys, such as, for example, nickel, copper, aluminum, silver and/or gold, metal-coated particles, such as, for example, silver-coated copper, silver-coated nickel and/or silver-coated glass microspheres, inorganic substances, such as, for example, barium titanium trioxide, strontium titanium trioxide, silicon dioxide, aluminum oxide, zinc oxide, titanium dioxide, manganese oxide, copper oxide, antimony oxide, molten silicon, **amorphous** molten silicon, ion-exchange resins, lithium-containing metal oxides, hollow glass microspheres, silicon sol-gel, titanium sol-gel and/or mixed titanium, carbon-based

substances, such as, for example, carbon, activated charcoal and/or diamond powder, elastomers, such as, for example, polybutadiene and/or polysiloxanes, semi-metals, and/or ceramic material can be used.

SUMM [0055] The transdermal therapeutic system may contain one or several members of the group of proton-pump inhibitors, such as omeprazole, **esomeprazole**, lansoprazol, leminoprazole, pantoprazole, rabeprazole, polaprezinc, and/or their derivatives and/or their pharmaceutically safe salts, as a component of the active substance.

CLM What is claimed is:
17. The cover layer that is impermeable to the active substances and/or a removable protective layer in accordance with claim 14, characterized in that nickel, copper, aluminum, silver and/or gold are used as a metal or alloy, silver-coated copper, silver-coated nickel, and/or silver-coated glass microspheres are used as metal-coated particles, barium titanium trioxide, strontium titanium trioxide, silicon dioxide, aluminum oxide, zinc oxide, titanium dioxide, manganese oxide, copper oxide, antimony oxide, molten or melted silicon, **amorphous** molten or **amorphous** melted silicon, ion-exchange resins, lithium-containing metal oxides, hollow glass microspheres, silicon sol-gel, titanium sol-gel, and/or mixed titanium are used as inorganic substances, carbon, activated charcoal and/or diamond powder are used as carbon-based substances, and/or polybutadiene and/or polysiloxanes are used as elastomers.

L2 ANSWER 16 OF 42 USPATFULL on STN
ACCESSION NUMBER: 2004:7871 USPATFULL
TITLE: Transmucosal delivery of proton pump inhibitors
INVENTOR(S): Widder, Kenneth, Rancho Santa Fe, CA, UNITED STATES
Hall, Warren, San Diego, CA, UNITED STATES
Olmstead, Kay, San Diego, CA, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2004006111	A1	20040108	
APPLICATION INFO.:	US 2003-353143	A1	20030127	(10)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 2002-351909P	20020125	(60)
	US 2002-374761P	20020422	(60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Richard H. Pagliery, Brobeck, Phleger & Harrison LLP, 12390 El Camino Real, San Diego, CA, 92130-2081
NUMBER OF CLAIMS: 90
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 1 Drawing Page(s)
LINE COUNT: 1161
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to pharmaceutical compositions and methods for transmucosal delivery of proton pump inhibitors. In one embodiment, the pharmaceutical composition of the present invention comprises a core which comprises an antacid, and an outer layer surrounding the core. The outer layer contains a therapeutically effective amount of a proton pump inhibitor. In another embodiment, the pharmaceutical composition of the present invention comprises an outer layer which comprising a unidirectional film, and an inner layer which contains a therapeutically effective amount of a proton pump inhibitor. In yet another embodiment, the pharmaceutical composition of the present invention is a

unidirectional tablet for delivery of a proton pump inhibitor across the oral mucosa. In this embodiment, the pharmaceutical composition contains an outer layer which contains a pharmaceutically acceptable water impermeable layer, and an inner layer which contains a therapeutically effective amount of a proton pump inhibitor.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM [0003] Proton pump inhibitors, also know as gastric H+/K+ inhibitors, are potent suppressors of gastric acid secretion. Over the past decade, they have been found to be the most effective drugs in antiulcer therapy (Goodman & Gilman's The Pharmacological Basis of Therapeutics (Joel G. Hardman et al. eds., 2001)). Currently available for clinical use are proton pump inhibitors such as omeprazole (PRILOSEC®), lansoprazole (PREVACID®), rabeprazole (ACIPHEX®)), pantoprazole (PROTONIX®) and **esomeprazole** (NEXIUM®). These proton pump inhibitors are a-pyridylmethylsulfinyl benzimidazoles with different substitutions on the pyridine or the benzimidazole groups.

SUMM [0005] Proton pump inhibitors are unstable at low pH and thus are typically supplied as enteric-coated granules encapsulated in a gelatin capsule (omeprazole, **esomeprazole**, and lansoprazole), as enteric-coated tablets (pantoprazole and rabeprazole), or as multiple pellet systems (**esomeprazole**-MUPS, omeprazole-MUPS). The enteric coating dissolves only upon exposure to a neutral to mildly alkaline pH, thus preventing degradation of the drugs by acid in the esophagus and stomach. Once absorbed from the small intestines, proton pump inhibitors are extensively metabolized in the liver by the cytochrome P450 system.

DETD [0029] A "proton pump inhibitor" or "PPI" refers to any substituted benzimidazole possessing pharmacological activity as an inhibitor of H+/H+ ATPase. Examples of PPIs suitable to be used in this invention include omeprazole, hydroxyomeprazole, **esomeprazole**, lansoprazole, pantoprazole, rabeprazole, dontoprazole, habeprazole, perprazole (**s-omeprazole** magnesium), ransoprazole, pariprazole, and leminoprazole in neutral form, as well as the pharmaceutically acceptable salt, prodrug, derivative, enantiomer, isomer, free base, anhydrate, hydrate, solvate, polymorph or combinations thereof, whether in crystalline form, **amorphous** form or a combination thereof, of such proton pump inhibitor.

DETD [0034] Examples of "excipients" suitable for the present invention include acacia, alginic acid, croscarmellose, gelatin, gelatin hydrosylate, mannitol, plasdone, sodium starch glycolate, sorbitol, sucrose, and xylitol. Specifically for molded or compressed tablet formulations, suitable excipients that may be used include **amorphous** lactose, beta lactose, microcrystalline cellulose, croscarmellose sodium, dicalcium phosphate, carboxymethyl cellulose, hydroxypropyl cellulose, polyethylene gylcols, sodium lauryl sulfate, and the like.

DETD [0050] Proton pump inhibitors that may be used include any substituted benzimidazole. Typically the proton pump inhibitor is selected from omeprazole, hydroxyomeprazole, **esomeprazole**, lansoprazole, pantoprazole, rabeprazole, dontoprazole, habeprazole, perprazole (**s-omeprazole** magnesium), ransoprazole, pariprazole, and leminoprazole in neutral form, as well as the pharmaceutically acceptable salt, prodrug, derivative, enantiomer, isomer, free base, anhydrate, hydrate, solvate, polymorph or combinations thereof, whether in crystalline form, **amorphous** form or a combination thereof, of such proton pump inhibitor. The proton pump inhibitor may be in a dosage form such as a powder, tablet, microspheres, or enteric-coated granules.

CLM What is claimed is:

2. The pharmaceutical composition of claim 1, wherein the proton pump inhibitor is selected from the group of omeprazole, hydroxyomeprazole, **esomeprazole**, lansoprazole, pantoprazole, rabeprazole, dontoprazole, habeprazole, perprazole, ransoprazole, pariprazole, leminoprazole, and pharmaceutically acceptable salts, prodrugs, derivatives, enantiomers, free bases, isomers, polymorphs, hydrates, anhydrates and solvates thereof.

4. The pharmaceutical composition of claim 2, wherein the proton pump inhibitor is lansoparazole, rabeprazole, pantoprazole, or **esomeprazole**, or a pharmaceutically acceptable salt, prodrug, derivative, enantiomer, free base, isomer, polymorph, hydrate, anhydrate or solvate thereof.

26. The pharmaceutical composition of claim 25, wherein the proton pump inhibitor is selected from the group of omeprazole, hydroxyomeprazole, **esomeprazole**, lansoprazole, pantoprazole, rabeprazole, dontoprazole, habeprazole, perprazole, ransoprazole, pariprazole, leminoprazole, and pharmaceutically acceptable salts, prodrugs, derivatives, enantiomers, free bases, isomers, polymorphs, hydrates, anhydrates and solvates thereof.

28. The pharmaceutical composition of claim 26, wherein the proton pump inhibitor is lansoparazole, rabeprazole, pantoprazole, or **esomeprazole** or a pharmaceutically acceptable salt, prodrug, derivative, enantiomer, free base, isomer, polymorph, hydrate, anhydrate or solvate thereof.

55. The pharmaceutical composition of claim 54, wherein the proton pump inhibitor is selected from the group of omeprazole, hydroxyomeprazole, **esomeprazole**, lansoprazole, pantoprazole, rabeprazole, dontoprazole, habeprazole, perprazole, ransoprazole, pariprazole, leminoprazole, and pharmaceutically acceptable salts, prodrugs, derivatives, enantiomers, free bases, isomers, polymorphs, hydrates, anhydrates and solvates thereof.

57. The pharmaceutical composition of claim 55, wherein the proton pump inhibitor is lansoparazole, rabeprazole, pantoprazole, or **esomeprazole** or a pharmaceutically acceptable salt, prodrug, derivative, enantiomer, free base, isomer, polymorph, hydrate, anhydrate or solvate thereof.

L2 ANSWER 17 OF 42 USPATFULL on STN
ACCESSION NUMBER: 2003:330646 USPATFULL
TITLE: Magnesium salt of **S-omeprazole**
INVENTOR(S): Sherman, Bernard Charles, Toronto, CANADA

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003232861	A1	20031218
APPLICATION INFO.:	US 2003-439233	A1	20030516 (10)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2002-129622, filed on 9 May 2002, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	CA 2002-2386716	20020517

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: IVOR M. HUGHES, BARRISTER & SOLICITOR,, PATENT & TRADEMARK AGENTS, 175 COMMERCE VALLEY DRIVE WEST, SUITE

200, THORNHILL, ON, L3T 7P6
NUMBER OF CLAIMS: 32
EXEMPLARY CLAIM: 1
LINE COUNT: 488
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A process of producing the magnesium salt of an enantiomer of omeprazole, said process comprising the steps of:

i) reacting magnesium with a lower alcohol to produce magnesium alkoxide in solution in the lower alcohol as solvent,

ii) adding the neutral form of the enantiomer of omeprazole to the solution, and

iii) flash-evaporating the solvent.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI Magnesium salt of **S-omeprazole**
SUMM [0002] The present invention relates to an improved form of the magnesium salt of **S-omeprazole**, a process for making same, and pharmaceutical compositions thereof.

SUMM [0005] The terms "omeprazole, **S-omeprazole** and R-omeprazole" as used in this specification designate the neutral form thereof, that is the form without a salt-forming cation present, unless otherwise indicated.

SUMM [0013] Omeprazole is a sulfoxide and a chiral compound, wherein the sulfur atom is the stereogenic center. Thus, omeprazole is a racemic mixture of its two single enantiomers, the R and S-enantiomer of omeprazole, herein referred to as R-omeprazole and **S-omeprazole**. The absolute configurations of the enantiomers of omeprazole have been determined by an X-ray study of an N-alkylated derivative of the (+)-enantiomer in non-salt form. The (+)-enantiomer of the non-salt form and the (-)-enantiomer of the non-salt form were found to have R and S configuration, respectively, and the (+)-enantiomer of the magnesium salt and the (-)-enantiomer of the magnesium salt were also found to have R and S configuration, respectively. The conditions for the optical rotation measurement for each of these enantiomers are described in WO 94/27988.

SUMM [0015] WO 96/02535 discloses a process for the preparation of the single enantiomers of omeprazole and salts thereof, and WO 96/01623 discloses a suitable tableted dosage form for instance magnesium salts of R- and **S-omeprazole**. The magnesium salt of **S-omeprazole** trihydrate described is substantially free from magnesium salts of R-omeprazole.

SUMM [0016] U.S. Pat. No. 5,714,504 describes optically pure salts of omeprazole and in particular the sodium and magnesium salts thereof as pure crystalline enantiomeric salts, and in one embodiment optically pure crystalline magnesium salts. The patent describes the non-aqueous process for the preparation of crystalline forms of the magnesium salts of optically pure enantiomers of omeprazole or analogues thereof; which include the steps of stirring a crude preparation of the omeprazole enantiomer under nitrogen into a methanolic magnesium methoxide solution, precipitating inorganic magnesium salts with the addition of a small amount of water, removing any precipitated inorganic magnesium salts, concentrating the residual methanolic solution, precipitating the omeprazole enantiomer by adding acetone to the residual solution, and filtering off the optically pure enantiomer crystals of magnesium omeprazole or analogues thereof. Because it is possible to purify

optically impure or partially pure salts of the enantiomers of omeprazole by crystallization, they can be obtained in very high optically pure, namely greater than or equal to 99.8% enantiomeric excess. Example 6 within the specification describes the preparation of the magnesium salt of **S-omeprazole** by crystallization of said salt.

SUMM [0017] The preferred enantiomer of omeprazole referred to as the (-)-enantiomer of omeprazole or a pharmaceutical salt thereof, is said to be an improved alternative to omeprazole in the treatment of gastric acid related diseases which provides higher dose efficiencies and less inter-individual variation in plasma levels, both between rapid and slow metabolizers and within the group of rapid metabolizers, as taught in U.S. Pat. No. 5,877,192. The major emphasis described relates to various forms of the enantiomers of omeprazole and salts thereof in crystalline form and preferably in highly crystalline form, which are also described in Canadian Patent Application No. 2,357,744. Although **amorphous** forms are nominally discussed there is no specific teaching as to the advantages of preventing crystals from forming. Therefore, a need exists for the magnesium salts of enantiomers of omeprazole having a desirable low methanol content.

SUMM [0018] U.S. Pat. No. 6,262,085 teaches in example 20 the magnesium salt of **S-omeprazole**. Generally, the patent describes the preferred crystalline form but states that other forms such as **amorphous** forms are casually mentioned, but clearly the teaching refers to crystalline and particularly to the co-crystalline form wherein enantiomers of omeprazole are present in the same crystal lattice and co-crystallized from solution. However, there is no teaching as to the manner in which **amorphous** forms in particular might be prepared, resulting in the same deficiencies with reference to solvent content as described above.

SUMM [0019] It would therefore be highly desirable to provide primarily **amorphous** magnesium salt of the enantimers of omeprazole and particularly the magnesium salt of **S-omeprazole**, since these salts have surprisingly high stability in alkaline conditions. There still exists a need for magnesium salts of enantiomers of omeprazole having substantially low methanol content and having a minimum amount of crystallinity with a large percentage of the material being **amorphous**, that is having minimum crystalline structure.

SUMM [0021] In light of the foregoing, the object of the present invention is to produce magnesium omeprazole and the magnesium salt of enantiomers of omeprazole having acceptably low levels of methanol, but containing a large proportion of **amorphous** material (non-crystalline), which preferably may also be substantially **amorphous** as well, to be produced by a simple process.

SUMM [0022] It is also an object of this invention to provide the magnesium salt of **S-omeprazole** in pharmaceutically acceptable forms.

SUMM [0025] According to one aspect of the invention magnesium omeprazole of the present invention is made by reacting magnesium in a lower alcohol to form magnesium alkoxide, preferably adding omeprazole in a quantity of about two moles per mole of magnesium, and flash-evaporating the alcohol, so as to form a solid precipitate without allowing the growth of crystals or particles that entrap the alcohol at unacceptable levels. The resulting material is substantially **amorphous** (non-crystalline).

SUMM [0026] According to a primary aspect of the invention the magnesium salt of the enantiomers of omeprazole of the present invention is made by reacting magnesium in a lower alcohol to form magnesium alkoxide, adding only one of the enantiomers of omeprazole in neutral form, for example **S-omeprazole**, or alternatively R-omeprazole, preferably in a quantity of about 2 moles per mole of magnesium, and flash evaporating the alcohol, so as to form a solid precipitate without allowing the substantial growth of crystals or particles that entrap the alcohol at unacceptable levels. The resulting material contains a desirable level of non-crystalline material, and preferably a primarily **amorphous** amount of the magnesium salts of either of the enantiomers of omeprazole, and preferably magnesium **S-omeprazole**. In another embodiment a substantially **amorphous** form is provided.

SUMM [0031] In one embodiment the enantiomer is **S-omeprazole**. In another embodiment the enantiomer is R-omeprazole. Preferably the lower alcohol is methanol.

SUMM [0033] According to yet another aspect of the invention there is provided magnesium **S-omeprazole** or alternatively magnesium R-omeprazole having a residual organic solvent content of less than 7% by weight.

SUMM [0034] According to yet another aspect of the invention there is provided magnesium **S-omeprazole** or alternatively magnesium R-omeprazole having a degree of crystallinity of under 67% and in one embodiment having a residual organic solvent content of less than 7% by weight, preferably a residual organic solvent content of less than 5% by weight, more preferably a residual organic solvent content of less than 2% by weight, and most preferably a residual organic solvent content of less than 1% by weight.

SUMM [0035] In one embodiment magnesium **S-omeprazole** or alternatively magnesium R-omeprazole has a degree of crystallinity of under 60%, preferably has a degree of crystallinity of under 50%, more preferably has a degree of crystallinity of under 25%.

SUMM [0036] Preferably a solid pharmaceutical composition for oral administration may further comprise magnesium **S-omeprazole** or alternatively magnesium R-omeprazole as described above, preferably in the form of a tablet, wherein the tablet may be enteric coated. In one embodiment the enteric coated tablet may further comprise a separating layer between said enteric coating and said tablet.

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SUMM [0037] The resulting composition comprising magnesium **S-omeprazole** or alternatively magnesium R-omeprazole is preferably in substantially **amorphous** form.

SUMM [0038] In the process of manufacture of magnesium omeprazole, or the magnesium salt of **s-omeprazole** according to one aspect of the present invention, magnesium is reacted in a lower alcohol, preferably methanol, to form a solution of magnesium alkoxide in the alcohol.

SUMM [0039] The atomic weight of magnesium is 24.3 and the molecular weight of omeprazole or the neutral form of **s-omeprazole** is 345.4. Since magnesium is divalent, the amount of magnesium required to convert 345.4 grams of omeprazole or **S-omeprazole** to magnesium omeprazole or the magnesium salt of **s-omeprazole** is 12.15 grams.

SUMM [0040] Hence 35.2 grams of magnesium is needed to convert 1 kilo of omeprazole or the neutral form of **s-omeprazole** to magnesium omeprazole or magnesium **s-omeprazole.**

SUMM [0041] The process of converting 1 kilo of omeprazole or the neutral form of **s-omeprazole** to magnesium omeprazole or the magnesium salt of **s-omeprazole**, thus begins with reacting 35.2 grams of magnesium in a lower alcohol, preferably methanol. The minimum amount of methanol needed to react fully and dissolve 35.2 grams of magnesium is about 1000 grams.

SUMM [0043] The omeprazole or the neutral form of **s-omeprazole** can then be added directly to the magnesium alkoxide solution. Alternatively, the omeprazole or the **s-omeprazole** (neutral form) may first be dissolved in an alcohol or another organic solvent that is miscible with the alcohol used to make the magnesium alkoxide, and the resultant solution may then be added to the magnesium alkoxide solution.

SUMM [0044] Where methanol is used as the sole solvent, a total of only about 1.5 kilos is needed for converting 1 kilo of omeprazole or the neutral form of **s-omeprazole** to magnesium omeprazole or the magnesium salt of **S-omeprazole.**

SUMM [0045] Hence, using quantities based on 1 kilo of omeprazole or **S-omeprazole** (or alternatively R-omeprazole), the simplest and best procedure is to react 35.2 grams of magnesium in about 1.5 kilos of methanol, wait until the magnesium has been fully reacted, and then adding 1 kilo of omeprazole or **S-omeprazole** to the solution and stir to dissolve. The result will be a solution of magnesium omeprazole or **S-omeprazole** equivalent to 1 kilo of omeprazole in methanol.

SUMM [0046] In order to obtain solid, magnesium omeprazole or magnesium **S-omeprazole** that is substantially free of organic solvent (i.e. substantially free of methanol, if methanol is used), it is then necessary to eliminate the solvent.

SUMM [0048] One method of flash-evaporating the solvent is to mix the solution into a solid excipient such as, for example, microcrystalline cellulose or the like, or any other well known appropriate excipient, so that a damp mass is formed. The mass can then be dried in a conventional oven, a fluid bed drier, or under vacuum to remove the solvent. Because the solution has been dispersed throughout the solid excipient, as the solvent evaporates, the magnesium omeprazole or the magnesium salt of **S-omeprazole**, is deposited as a thin layer over the surface of the particles of the solid excipient and does not precipitate as crystals or large granules, so that there is little or no entrapment of solvent.

SUMM [0050] It has been found in utilizing the above-mentioned preferred processes that magnesium omeprazole and the magnesium salt of **S-omeprazole** can be made having a residual solvent content substantially lower than can be achieved by simply evaporating the solvent from the solution under vacuum.

SUMM [0051] The residual organic solvent content by weight of the magnesium omeprazole, and the magnesium salt of **S-omeprazole** made according to the present invention will be under 7%, preferably under 5%, more preferably under 2%, and most preferably under 1%.

SUMM [0055] A=the area between the peaks and the background ("the **amorphous** area").

SUMM [0057] The degree of crystallinity of magnesium omeprazole and the magnesium salt of **S-omeprazole** according to the present invention is under 67%, as compared to 67% or higher for magnesium omeprazole crystalline dihydrate according to the prior art.

SUMM [0059] If the magnesium omeprazole or the magnesium salt of **S-omeprazole** of the present invention is made in an environment and using excipients (including the air or other gas used for drying in the spray-dry process) that is completely free of water, the magnesium omeprazole or the magnesium **S-omeprazole** will be anhydrous. However, pure anhydrous magnesium omeprazole or magnesium **S-omeprazole** is hygroscopic and it will readily absorb water from air until it reaches an equilibrium water content of about 5% to 8%, depending on the relative humidity of the air. This is not problematic, as it does not adversely affect stability of the final product.

SUMM [0060] The present invention will be further processed into pharmaceutical compositions such as, for example, tablets for oral administration. The tablets will preferably be enteric coated to protect the magnesium omeprazole and magnesium **S-omeprazole** from the effects of gastric acid.

DETD [0063] The next morning it was observed that the magnesium had all been consumed and that the effervescence had ceased, resulting in a slightly hazy solution of magnesium methoxide in methanol. 50 grams of omeprazole (or the neutral form of **S-omeprazole** could be used) was then added to the contents of the flask and the contents were stirred for several minutes until dissolved to form a solution of magnesium omeprazole (or if the neutral form of **S-omeprazole** was used, magnesium **S-omeprazole**) in methanol.

DETD [0066] The resulting dry material was a fine powder, which appeared non-crystalline (i.e. **amorphous**) and also had no evident odour of residual methanol. The powder was tested to determine the level of residual methanol, which was found to be 0.7%.

DETD [0067] This powder was examined for crystallinity by powder X-ray diffraction, and it was found that the powder was primarily **amorphous** (non-crystalline), having a degree of crystallinity of under 25%.

DETD [0068] The following ingredients are to be mixed together in the proportions shown:

Magnesium **S-omeprazole** (prepared according to Examples 1 and 3)	21.0
Anhydrous lactose	131.0
Croscarmellose sodium	6.4
Magnesium stearate	1.6
	160.0

DETD [0069] The mixture is to be compressed into tablets having a weight of 160 mg per tablet, so that each tablet will contain 21 mg of magnesium **S-omeprazole**, which is equivalent to about 20 mg of omeprazole.

CLM What is claimed is:

2. The process of claim 1 wherein the enantiomer is **S-omeprazole.**

6. Magnesium **S-omeprazole** having a residual organic

solvent content of less than 7% by weight.

7. Magnesium **S-omeprazole** having a degree of crystallinity of under 67%.

8. Magnesium **S-omeprazole** of claim 7 having a residual organic solvent content of less than 7% by weight.

9. Magnesium **S-omeprazole** of claim 6 or 7 having a residual organic solvent content of less than 5% by weight.

10. Magnesium **S-omeprazole** of claim 6 or 7 having a residual organic solvent content of less than 2% by weight.

11. Magnesium **S-omeprazole** of claim 6 or 7 having a residual organic solvent content of less than 1% by weight.

12. Magnesium **S-omeprazole** of claims 6, or 7 only having a degree of crystallinity of under 60%.

13. Magnesium **S-omeprazole** of claims 6, or 7 only having a degree of crystallinity of under 50%.

14. Magnesium **S-omeprazole** of claims 6, or 7 only having a degree of crystallinity of under 25%.

15. A solid pharmaceutical composition for oral administration comprising magnesium **S-omeprazole** of claims 6, or 7 only.

30. The composition of claim 6, or 7 only wherein magnesium **S-omeprazole** is in substantially **amorphous** form.

31. The composition of claim 18, or 19 only wherein magnesium R-omeprazole is in substantially **amorphous** form.

L2 ANSWER 18 OF 42 USPATFULL on STN
ACCESSION NUMBER: 2003:329809 USPATFULL
TITLE: Particulate materials
INVENTOR(S): York, Peter, Ilkley, UNITED KINGDOM
Shekunov, Boris Yu, Aurora, OH, UNITED STATES
Rehman, Mahboob Ur, Leeds, UNITED KINGDOM
Feeley, Jane Catherine, Bradford, UNITED KINGDOM

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2003232020	A1	20031218	
APPLICATION INFO.:	US 2003-422342	A1	20030424	(10)

	NUMBER	DATE
PRIORITY INFORMATION:	GB 2002-9402	20020424
	GB 2002-10174	20020503
	GB 2002-10268	20020507
	GB 2002-11086	20020515

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: NEKTAR THERAPEUTICS, 150 INDUSTRIAL ROAD, SAN CARLOS, CA, 94070
NUMBER OF CLAIMS: 43
EXEMPLARY CLAIM: 1

NUMBER OF DRAWINGS: 12 Drawing Page(s)
LINE COUNT: 2386
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to active substances in particulate form, to methods for preparing them and to their uses. The present invention provides particulate powders, such as might be of use for delivery using a dry powder inhaler (DPI) or similar delivery device, having properties which may be beneficial to the DPI delivery process.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD [0084] An active substance according to the invention may have an **amorphous** content of less than 5% w/w, preferably less than 2% w/w, more preferably less than 1 or even than 0.5 or 0.2% w/w. Ideally its **amorphous** phase content is at least 10 times, preferably at least 20 or even 40 or 50 times, lower than that of the same active substance produced by a non-SEDS.TM. particle formation process.

DETD [0108] The active substance of the invention is preferably in the form of solid (eg, as opposed to hollow, porous or at least partially fluid-containing) particles. It is preferably in a crystalline or semi-crystalline (as opposed to **amorphous**) form, more preferably crystalline.

DETD [0124] In certain cases, an active substance according to the present invention may be a pharmaceutically active substance or a pharmaceutically acceptable excipient (preferably a substance suitable for and/or intended for delivery by inhalation) other than salmeterol xinafoate (alone or coformulated with hydroxypropyl cellulose); ct-lactose monohydrate; R-TEM β-lactamase; maltose; trehalose; sucrose; budesonide; salbutamol sulphate; nicotinic acid; paracetamol (alone or coformulated with salmeterol xinafoate, L-poly(lactic acid), ethyl cellulose (EC), hydroxypropyl methyl cellulose (HPMC) or poly vinyl pyrrolidone (PVP)); ibuprofen; ketoprofen (alone or coformulated with EC, HPMC or PVP); salicylic acid; either indomethacin, carbamazepine, theophylline, ascorbic acid or a COX-2 selective inhibitor coformulated with EC, HPMC or PVP; quinine sulphate coformulated with EC; fluticasone propionate; omeprazole magnesium tetrahydrate; (S)-**omeprazole** magnesium trihydrate; formoterol fumarate dihydrate; felodipine; candesartan cilexetil; lysozyme; albumin; insulin; terbutaline sulphate; fenoterol hydrobromide; dihydroergotamine mesylate; and/or risperidone-(9-hydroxy)-palmitate.

DETD [0190] The mean **amorphous** content of the micronised sample, determined by the dynamic moisture sorption method, was 6.92%, w/w (standard deviation 1.10). That of the SEDS.TM. sample in contrast was only 0.13% w/w (SD 0.05).

DETD [0231] TBS was produced using the SEDS.TM. process. Different solvents such as pure methanol, methanol/water, pure water and pure ethanol were used to dissolve drug material between 1-10% w/v in concentration. To optimise the particle properties (crystallinity, shape, size, size distribution) a number of parameters such as concentration of the drug, drug solution flow rate, CO.sub.2 flow rate, temperature and pressure of the system were manipulated. A wide range of SEDS.TM. products such as a hydrated crystal, **amorphous** material, and two previously reported polymorphs A and B were produced using different solvents and experimental conditions, as seen in FIGS. 5a-f. For example, the clear difference in morphology and crystallinity (determined by XRPD which was based on diffraction peaks area and DSC by measuring change in enthalpy of fusion) of TBS1 (127.12 J/g) and TBS2 (88.68 J/g) may be attributed primarily to the different residence time for particle formation and mixing in vessels which is defined as $\tau=V/f$, where V is the volume of the vessel and f is the volumetric flow rates of ethanol and CO.sub.2 at given temperature and pressure respectively. Particles in the smaller 50 ml vessel were exposed to partially mixed ethanol-rich phase which

exist in the core of high velocity jet (B. Y. Shekunov, J. Baldyga, and P. York. Particle formation by mixing with supercritical antisolvent at high Reynolds numbers, Chem. Eng. Sci., 56: 2421-2433 (2001)), whereas the particles in the large 500 ml vessel were accumulated in well mixed CO.sub.2 -rich phase.

DETD [0232] SEM photomicrographs of a typical micronised and SCF processed batches of TBS are shown in FIGS. 5a-f. The use of different solvents such as pure methanol and methanol/water resulted in needle-like as well as-spherical **amorphous** particles respectively. Particles obtained using pure methanol, pure ethanol and pure water have revealed well-defined crystal edges compared to micronised particles.

DETD [0235] The samples were also analysed with the AeroSizer.TM.. Micronised, TBS1 and TBS2 samples have similar aerodynamic diameters to those obtained by the Sympatec.TM. laser diffraction instrument. However, TBS3, TBS4 and TBS5 showed larger mean diameters by AeroSizer.TM. in comparison to laser diffraction analysis. These results are depicted in Table 7 below. The AeroSizer.TM. gives an aerodynamic equivalent diameter, which is smaller than geometric volume diameter for non-spherical primary particles. Therefore, the results here likely indicate insufficient dispersion by AeroDisperser.TM. of the agglomerated particles of both batches TBS4 and TBS5 (FIG. 5e,f). In addition, the sampling procedures in the AeroSizer.TM. nozzle may produce discrepancies in time-of-flight measurements at large particle number densities, which is the case of small **amorphous** particles in FIG. 5e. Therefore, the reproducibility of results for this technique was lower than for the laser diffraction method.

TABLE 7

Sample	Sympatec D.sub.4,3 (μm)	Aerosizer D.sub.4,3 (μm)
Micronised	3.04	2.69
TBS 1	3.22	3.31
TBS 2	3.43	3.44
TBS 3	1.99	6.69
TBS 4	4.75	15.53
TBS 5	4.84	11.44

DETD [0237] The X-ray powder patterns in FIGS. 6a-c illustrate the crystallinity of micronised and TBS1 and TBS2 samples, which is assessed on the basis of the sharpness of the major diffraction peaks. From the results it can be seen that there is no significant difference in the XRPD profiles of micronised and TBS1 samples. However, based on XRPD data, the TBS2 sample has shown lower bulk crystallinity in comparison to the micronised sample. The DSC profiles (Table 8) confirm this conclusion; the fusion enthalpy for TBS2 batch is considerably lower than for both micronised and TBS1 batches, thus the crystallinity for TBS1 being higher than that for the micronised material.

TABLE 8

Sample	Melting Point (° C.)	Enthalpy of Fusion (J/g)	Identification
Micronised	266.3	121.76	Form B
TBS 1	267.1	127.12	Form B
TBS 2	266.3	88.68	Form B
TBS 3	266.3	31.35	**Amorphous**
TBS 4	274.5	40.98	Hydrate
TBS 5	272.7	57.69	Form A

DETD [0239] The sorption and desorption isotherms of micronised and SC

processed TBS show that at 25° C., the equilibrium moisture content ("moisture uptake") of all TBS samples in this study is very low (<0.4%) at any RH value. The low moisture uptake indicates that each powder is crystalline. However, TBS2 sample showed slightly higher moisture uptake than the micronised sample, which is consistent with its lower bulk crystallinity indicated by DSC and X-ray diffraction (see FIG. 6 and Table 8). Typically, an **amorphous** or partially crystalline material will take up more moisture than a highly crystalline material. TBS2 also takes up more moisture at relative humidities beyond 90% RH. Under these conditions, the sample may be deliquescing at high RH.

DETD [0240] In FIG. 7, the heat flow (μW) for both micronised and SEDS.TM. powders of TBS are normalised to 1 mg for comparison. The endothermic peak for micronised TBS is most likely due to crystallisation of the **amorphous** fraction that was previously induced by micronisation. The TAM profile for TBS2 sample of TBS has an incomplete exothermic peak between 85 and 90% RH because the RH ramping experiment (3% RH/hr from 0% to 90% RH) ended before the event was completed. No exothermic or endothermic peaks were observed in the TAM profile of TBS1 sample of TBS, which is typical for a highly crystalline material. The TAM results show that the micronised TBS has an event at about 79% RH, probably due to crystallisation. The results also show that TBS2 sample has an exothermic event at about 85% RH.

CLM What is claimed is:

26. An active substance of claim 1 further comprising an **amorphous** phase content which is at least 10 times lower than that for particles of the same active substance made by micronisation, granulation, or solvent crystallization.

30. An active substance of claim 1 further comprising an **amorphous** phase content of less than 1% w/w.

L2 ANSWER 19 OF 42 USPATFULL on STN

ACCESSION NUMBER:	2003:319388 USPATFULL
TITLE:	DRY BLEND PHARMACEUTICAL FORMULATIONS
INVENTOR(S):	Whittle, Robert R., Wilmington, NC, UNITED STATES Sancilio, Frederick D., Wilmington, NC, UNITED STATES Stowell, Grayson Walker, Wilmington, NC, UNITED STATES Jenkins, Douglas John, Wilmington, NC, UNITED STATES Whittall, Linda B., Wilmington, NC, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003225137	A1	20031204
	US 6667324	B2	20031223
APPLICATION INFO.:	US 2003-439438	A1	20030516 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2002-189659, filed on 3 Jul 2002, PENDING Continuation of Ser. No. US 2002-57659, filed on 25 Jan 2002, GRANTED, Pat. No. US 6444689 Continuation of Ser. No. US 2000-645145, filed on 24 Aug 2000, GRANTED, Pat. No. US 6369087 Continuation-in-part of Ser. No. US 2000-519976, filed on 7 Mar 2000, GRANTED, Pat. No. US 6262085

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-150878P	19990826 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	MYERS BIGEL SIBLEY & SAJOVEC, PO BOX 37428, RALEIGH, NC, 27627

10/690,897

NUMBER OF CLAIMS: 64
EXEMPLARY CLAIM: 1
LINE COUNT: 4113
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Compounds represented by formula (Ia) are disclosed by the invention, along with compositions and complexes thereof, optionally in combination with compounds of formula (Ib). Pharmaceutical formulations and methods of making and using such compounds are also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM [0010] The teachings regarding the methods of making omeprazole as referred to in these references, salts thereof, enantiomers thereof, and salts of the enantiomers, as well as formulations which may include these compounds, all rely on the chemical structure of omeprazole being accurately determined and the referenced compound or compounds being consistently prepared using the referenced techniques. More specifically, a methoxy group on the benzimidazole ring has been explicitly stated in the literature to be present at the 5-position, in omeprazole, a racemic mixture, and an optically pure isomer of omeprazole designated as **esomeprazole** or **s-omeprazole**. Applicants have now unexpectedly discovered the complexity of omeprazole and the relative bioactivity of each of its previously undiscovered and undisclosed attributes. More specifically, Applicants have confirmed that the methods of the prior art do not yield a single compound having the methoxy group in the 5-position on the benzimidazole ring as previously taught, nor do all of the methods of the prior art yield consistent results. In fact, omeprazole as conventionally referred to as a bulk drug substance (in its solid state) has been discovered to be present in the form of two pharmaceutically active compounds having the methoxy group on the benzimidazole ring at the 6- and 5-positions. Additionally, Applicants have discovered the presence of a second chiral location at the pyridine ring plane in each of the two compounds such that each compound has two positional isomers and four diastereomers. Therefore, the present invention provides these individual compounds, along with any salts, hydrates, solvates, combinations thereof, and polymorphs thereof, compositions of the abate, and methods of making the same that are not taught or suggested by the prior art, pharmaceutical formulations of the compounds, compositions, and complexes of the present invention, and methods for using the same.

SUMM [0073] Accordingly, methods of the present invention provide for improved biological activity/efficacy (e.g. inhibition of gastric acid secretions and, thus, treatment of gastric acid disturbances in mammals, including humans) of pharmaceutically active compounds omeprazole and **esomeprazole**, as presently known in the art comprising administering to such mammals in need of treatment a non-toxic, therapeutically effective amount of any composition of the present invention comprising compounds or compositions of the present invention having individual diastereomers comprising S.sub.xa--R.sub.4q; S.sub.xa--R.sub.4z; S.sub.xb--R.sub.4q; or S.sub.xb--R.sub.4z, or one or more pharmaceutically acceptable salts, solvates, hydrates, or combinations thereof. Also provided are such methods wherein said compounds or complexes of the present invention having said selected individual diastereomer pair essentially free of compounds of the present invention having diastereomer pairs other than said selected individual diastereomers. A preferred diastereomer is S.sub.xa--R.sub.4q, and an especially preferred diastereomer is S.sub.xa--R.sub.4z.

SUMM [0081] In another aspect, the invention also provides compositions of active pharmaceutical ingredient ("API") comprising any of the compounds, compositions, or complexes of the present invention, each of

which may be present in crystalline form, in part or in whole. Advantageously, each such compositions and/or complexes comprising compounds represented by formula (Ia) may also include any one or more of the specific compounds represented by formulae (Iai), (Iaii), (Iaiii), and (Iaiv), or pharmaceutically acceptable salts, solvates, hydrates, polymorphs, or combinations thereof, whether in crystalline form, **amorphous** form, or a combination thereof. Each can be used as the bases for any such API composition.

SUMM [0142] Any of such composition embodiments comprising any of the compounds represented by formulae (Ia) and (Ib), individual species of compounds (Iai)-(Ibi), (Iaii)-(Ibii), (Iaiii)-(Ibiii), and (Iaiv)-(Ibiv), diastereomers thereof, or one or more pharmaceutically acceptable salts, solvates, hydrates, or combinations thereof, may be present in crystalline form, **amorphous** form, or combinations thereof.

SUMM [0143] The invention also provides compositions of active pharmaceutical ingredient ("API") comprising any of the above composition embodiments. Advantageously, any of the compositions comprising compounds represented by formulae (Ia) and (Ib) may also comprise any of the specific compositions represented by formulae (Iai)-(Ibi); (Iaii)-(Ibii); (Iaiii)-(Ibiii); and (Iaiv)-(Ibiv) or one or more pharmaceutically acceptable salts, solvates, hydrates, polymorphs, or combinations thereof, whether in crystalline form, **amorphous** form, or a combination thereof, can be used in any such API compositions.

SUMM [0146] Additionally, when using such processes represented in the prior art, negligible or trace amounts of previously unknown compounds are formed as described herein. For example, in the preparation of such composition as referenced in the immediately preceding paragraph, compounds having the previously unknown diastereomers S.sub.xa--R.sub.4q and S.sub.xb--R.sub.4z are formed with varying and inconsistent ratios of compounds represented by formulae (Ia) and (Ib). Also formed in trace quantities, and typically in **amorphous** form, are compounds represented by formulae (Ia) and (Ib) having the previously unknown diastereomers S.sub.xa--R.sub.4z and S.sub.xb--R.sub.4q.

SUMM [0148] Accordingly, the processes taught in the prior art for the preparation of "omeprazole" as well as "**esomeprazole**" (the intended S-isomer of "omeprazole") provide quantities of previously unknown and unrecognized compounds having pharmaceutical activity, or that are used as intermediates in the preparation of pharmaceutically active compounds of the present invention, or that are used as prodrugs that convert to the active metabolite in vivo. Furthermore, many such processes do not invariably provide the same result when conducted as taught in the prior art.

SUMM [0175] By employing the above method(s) obtaining the compound represented by formula (Ia) in solid state, one obtains the (-) and (+) enantiomers as a racemic mixture, with these enantiomers including various amounts of diastereomers as set forth herein. In one embodiment, Applicants have discovered that the (-) and (+) enantiomers may be predominantly present as the S.sub.xa--R.sub.4q and S.sub.xb--R.sub.4z diastereomers respectively. Although not intending to be bound by theory, in this embodiment, the two molecules (i.e., compounds of formulae (Ia) and (Ib)) co-crystallize in a centric space group in which the molecules are related to each other through a center of inversion and linked by hydrogen bonding from the amine hydrogens to the sulfoxide oxygens. The R.sub.4 methoxy methyl is directed towards the center of the bridged complex. Examination of the contact distances in the region where the other methoxy methyl would presumably reside demonstrates that

there is not adequate space within the lattice for the other diastereomers (S.sub.xa--R.sub.4z and S.sub.xb--R.sub.4q) to co-exist. In this embodiment, the compound represented by formula (Ia) may comprise about 99 percent (w/w) of the S.sub.xb--R.sub.4z and S.sub.xa--R.sub.4q diastereomers and the remaining percentage of other components which may include, for example, the diastereomers S.sub.xa--R.sub.4z and S.sub.xb--R.sub.4q, generally in **amorphous** form.

SUMM [0181] Although not intending to be bound by theory, such compounds of formula (Ia) are believed to be crystalline with little **amorphous** content. However, when grinding is applied to a solid sample comprising the compound of formula (Ia), and in a preferred embodiment the compounds of formulae (Ia) and (Ib), an increase in the **amorphous** character of the sample is believed to result along with an increase in the amount of compound of formula (Ib). Again, not intending to be bound by theory, it is believed that the sample undergoes a solid state transformation and "recrystallizes" or transforms over a relatively short period of time from the more **amorphous** state to a more crystalline state subsequent to grinding. Nonetheless, it is believed that by performing multiple grinding steps in sequence, (i.e., grinding followed by relaxation followed by grinding) one may obtain a solid sample that becomes more **amorphous** in character and hence comprises a greater amount of the compound of the formula (Ib) as opposed to a sample that has experienced a lesser amount of grinding.

SUMM [0183] The structure of the compound of formula (Ib) can be confirmed by solid state techniques such as, for example, X-ray powder diffraction patterns, Raman, FTIR, solid state NMR, and thermal analysis, of the ground material and the unground material. For example, comparison of the two powder patterns showed distinct decreases in intensity, broadening of the peaks, and an increase in the **amorphous** nature for the ground material. The ground material showed a powder pattern that is more consistent with the proposed more **amorphous** nature of the compound of formula (Ib), e.g., 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

SUMM [0301] The following examples are intended to illustrate the invention, and are not to be construed as limiting the scope of the invention. For the purposes or the examples, the phrase "(5)6-methoxy 2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole" refers to a combination of, preferably a co-crystallized mixture, (with or without an amount of **amorphous** compounds), of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl]sulfinyl]-1H-benzimidazole and 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole, each as determined and referenced herein.

L2 ANSWER 20 OF 42 USPATFULL on STN
ACCESSION NUMBER: 2003:319387 USPATFULL
TITLE: Alkoxy substituted benzimidazole compounds, pharmaceutical preparations containing the same, and methods of using the same
INVENTOR(S): Whittle, Robert R., Wilmington, NC, UNITED STATES
Sancilio, Frederick D., Wilmington, NC, UNITED STATES
Stowell, Grayson Walker, Wilmington, NC, UNITED STATES
Jenkins, Douglas John, Wilmington, NC, UNITED STATES
Whittall, Linda B., Wilmington, NC, UNITED STATES

NUMBER KIND DATE

PATENT INFORMATION:	US 2003225136	A1	20031204
	US 6706737	B2	20040316
APPLICATION INFO.:	US 2003-434259	A1	20030508 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2002-189659, filed on 3 Jul 2002, PENDING Continuation of Ser. No. US 2002-57659, filed on 25 Jan 2002, GRANTED, Pat. No. US 6444689 Continuation of Ser. No. US 2000-645145, filed on 24 Aug 2000, GRANTED, Pat. No. US 6369087 Continuation-in-part of Ser. No. US 2000-519976, filed on 7 Mar 2000, GRANTED, Pat. No. US 6262085

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-150878P	19990826 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: MYERS BIGEL SIBLEY & SAJOVEC, PO BOX 37428, RALEIGH, NC, 27627
NUMBER OF CLAIMS: 64
EXEMPLARY CLAIM: 1
LINE COUNT: 4128
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compounds represented by formula (Ia) are disclosed by the invention, along with compositions and complexes thereof, optionally in combination with compounds of formula (Ib). Pharmaceutical formulations and methods of making and using such compounds are also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM [0010] The teachings regarding the methods of making omeprazole as referred to in these references, salts thereof, enantiomers thereof, and salts of the enantiomers, as well as formulations which may include these compounds, all rely on the chemical structure of omeprazole being accurately determined and the referenced compound or compounds being consistently prepared using the referenced techniques. More specifically, a methoxy group on the benzimidazole ring has been explicitly stated in the literature to be present at the 5-position, in omeprazole, a racemic mixture, and an optically pure isomer of omeprazole designated as **esomeprazole** or **s-omeprazole**. Applicants have now unexpectedly discovered the complexity of omeprazole and the relative bioactivity of each of its previously undiscovered and undisclosed attributes. More specifically, Applicants have confirmed that the methods of the prior art do not yield a single compound having the methoxy group in the 5-position on the benzimidazole ring as previously taught, nor do all of the methods of the prior art yield consistent results. In fact, omeprazole as conventionally referred to as a bulk drug substance (in its solid state) has been discovered to be present in the form of two pharmaceutically active compounds having the methoxy group on the benzimidazole ring at the 6- and 5-positions. Additionally, Applicants have discovered the presence of a second chiral location at the pyridine ring plane in each of the two compounds such that each compound has two positional isomers and four diastereomers. Therefore, the present invention provides these individual compounds, along with any salts, hydrates, solvates, combinations thereof, and polymorphs thereof, compositions of the abate, and methods of making the same that are not taught or suggested by the prior art, pharmaceutical formulations of the compounds, compositions, and complexes of the present invention, and methods for using the same.

SUMM [0073] Accordingly, methods of the present invention provide for improved biological activity/efficacy (e.g. inhibition of gastric acid secretions and, thus, treatment of gastric acid disturbances in mammals,

including humans) of pharmaceutically active compounds omeprazole and **esomeprazole**, as presently known in the art comprising administering to such mammals in need of treatment a non-toxic, therapeutically effective amount of any composition of the present invention comprising compounds or compositions of the present invention having individual diastereomers comprising S.sub.xa--R.sub.4q; S.sub.xa--R.sub.4z; S.sub.xb--R.sub.4q; or S.sub.xb--R.sub.4z, or one or more pharmaceutically acceptable salts, solvates, hydrates, or combinations thereof. Also provided are such methods wherein said compounds or complexes of the present invention having said selected individual diastereomer pair essentially free of compounds of the present invention having diastereomer pairs other than said selected individual diastereomers. A preferred diastereomer is S.sub.xa--R.sub.4q, and an especially preferred diastereomer is S.sub.xa--R.sub.4z.

SUMM [0081] In another aspect, the invention also provides compositions of active pharmaceutical ingredient ("API") comprising any of the compounds, compositions, or complexes of the present invention, each of which may be present in crystalline form, in part or in whole. Advantageously, each such compositions and/or complexes comprising compounds represented by formula (Ia) may also include any one or more of the specific compounds represented by formulae (Iai), (Iaii), (Iaiii), and (Iaiv), or pharmaceutically acceptable salts, solvates, hydrates, polymorphs, or combinations thereof, whether in crystalline form, **amorphous** form, or a combination thereof. Each can be used as the bases for any such API composition.

SUMM [0142] Any of such composition embodiments comprising any of the compounds represented by formulae (Ia) and (Ib), individual species of compounds (Iai)-(Ibi), (Iaii)-(Ibii), (Iaiii)-(Ibiii), and (Iaiv)-(Ibiv), diastereomers thereof, or one or more pharmaceutically acceptable salts, solvates, hydrates, or combinations thereof, may be present in crystalline form, **amorphous** form, or combinations thereof.

SUMM [0143] The invention also provides compositions of active pharmaceutical ingredient ("API") comprising any of the above composition embodiments. Advantageously, any of the compositions comprising compounds represented by formulae (Ia) and (Ib) may also comprise any of the specific compositions represented by formulae (Iai)-(Ibi); (Iaii)-(Ibii); (Iaiii)-(Ibiii); and (Iaiv)-(Ibiv) or one or more pharmaceutically acceptable salts, solvates, hydrates, polymorphs, or combinations thereof, whether in crystalline form, **amorphous** form, or a combination thereof, can be used in any such API compositions.

SUMM [0146] Additionally, when using such processes represented in the prior art, negligible or trace amounts of previously unknown compounds are formed as described herein. For example, in the preparation of such composition as referenced in the immediately preceding paragraph, compounds having the previously unknown diastereomers S.sub.xa--R.sub.4q and S.sub.xb--R.sub.4z are formed with varying and inconsistent ratios of compounds represented by formulae (Ia) and (Ib). Also formed in trace quantities, and typically in **amorphous** form, are compounds represented by formulae (Ia) and (Ib) having the previously unknown diastereomers S.sub.xa--R.sub.4z and S.sub.xb--R.sub.4q.

SUMM [0148] Accordingly, the processes taught in the prior art for the preparation of "omeprazole" as well as "**esomeprazole**" (the intended S-isomer of "omeprazole") provide quantities of previously unknown and unrecognized compounds having pharmaceutical activity, or that are used as intermediates in the preparation of pharmaceutically

active compounds of the present invention, or that are used as prodrugs that convert to the active metabolite in vivo. Furthermore, many such processes do not invariably provide the same result when conducted as taught in the prior art.

SUMM [0175] By employing the above method(s) obtaining the compound represented by formula (Ia) in solid state, one obtains the (-) and (+) enantiomers as a racemic mixture, with these enantiomers including various amounts of diastereomers as set forth herein. In one embodiment, Applicants have discovered that the (-) and (+) enantiomers may be predominantly present as the S.sub.xa--R.sub.4q and S.sub.xb--R.sub.4z diastereomers respectively. Although not intending to be bound by theory, in this embodiment, the two molecules (i.e., compounds of formulae (Ia) and (Ib)) co-crystallize in a centric space group in which the molecules are related to each other through a center of inversion and linked by hydrogen bonding from the amine hydrogens to the sulfoxide oxygens. The R.sub.4 methoxy methyl is directed towards the center of the bridged complex. Examination of the contact distances in the region where the other methoxy methyl would presumably reside demonstrates that there is not adequate space within the lattice for the other diastereomers (S.sub.xa--R.sub.4z and S.sub.xb--R.sub.4q) to co-exist. In this embodiment, the compound represented by formula (Ia) may comprise about 99 percent (w/w) of the S.sub.xb--R.sub.4z and S.sub.xa--R.sub.4q diastereomers and the remaining percentage of other components which may include, for example, the diastereomers S.sub.xa--R.sub.4z and S.sub.xb--R.sub.4q, generally in **amorphous** form.

SUMM [0181] Although not intending to be bound by theory, such compounds of formula (Ia) are believed to be crystalline with little **amorphous** content. However, when grinding is applied to a solid sample comprising the compound of formula (Ia), and in a preferred embodiment the compounds of formulae (Ia) and (Ib), an increase in the **amorphous** character of the sample is believed to result along with an increase in the amount of compound of formula (Ib). Again, not intending to be bound by theory, it is believed that the sample undergoes a solid state transformation and "recrystallizes" or transforms over a relatively short period of time from the more **amorphous** state to a more crystalline state subsequent to grinding. Nonetheless, it is believed that by performing multiple grinding steps in sequence, (i.e., grinding followed by relaxation followed by grinding) one may obtain a solid sample that becomes more **amorphous** in character and hence comprises a greater amount of the compound of the formula (Ib) as opposed to a sample that has experienced a lesser amount of grinding.

SUMM [0183] The structure of the compound of formula (Ib) can be confirmed by solid state techniques such as, for example, X-ray powder diffraction patterns, Raman, FTIR, solid state NMR, and thermal analysis, of the ground material and the unground material. For example, comparison of the two powder patterns showed distinct decreases in intensity, broadening of the peaks, and an increase in the **amorphous** nature for the ground material. The ground material showed a powder pattern that is more consistent with the proposed more **amorphous** nature of the compound of formula (Ib), e.g., 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

SUMM [0301] The following examples are intended to illustrate the invention, and are not to be construed as limiting the scope of the invention. For the purposes or the examples, the phrase "(5)6-methoxy 2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole" refers to a combination of, preferably a co-crystallized

mixture, (with or without an amount of **amorphous** compounds), of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl]sulfinyl]-1H-benzimidazole and 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole, each as determined and referenced herein.

L2 ANSWER 21 OF 42 USPATFULL on STN
ACCESSION NUMBER: 2003:319386 USPATFULL
TITLE: DRY-BLEND PHARMACEUTICAL FORMULATIONS
INVENTOR(S): Whittle, Robert R., Wilmington, NC, UNITED STATES
Sancilio, Frederick D., Wilmington, NC, UNITED STATES
Stowell, Grayson Walker, Wilmington, NC, UNITED STATES
Jenkins, Douglas John, Wilmington, NC, UNITED STATES
Whittall, Linda D., Wilmington, NC, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003225135	A1	20031204
	US 6667323	B2	20031223
APPLICATION INFO.:	US 2003-431019	A1	20030507 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2002-189659, filed on 3 Jul 2002, PENDING Continuation of Ser. No. US 2002-57659, filed on 25 Jan 2002, GRANTED, Pat. No. US 6444689 Continuation of Ser. No. US 2000-645145, filed on 24 Aug 2000, GRANTED, Pat. No. US 6369087 Continuation-in-part of Ser. No. US 2000-519976, filed on 7 Mar 2000, GRANTED, Pat. No. US 6262085

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-150878P	19990826 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: MYERS BIGEL SIBLEY & SAJOVEC, PO BOX 37428, RALEIGH, NC, 27627
NUMBER OF CLAIMS: 64
EXEMPLARY CLAIM: 1
LINE COUNT: 4119
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Compounds represented by formula (Ia) are disclosed by the invention, along with compositions and complexes thereof, optionally in combination with compounds of formula (Ib). Pharmaceutical formulations and methods of making and using such compounds are also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM [0010] The teachings regarding the methods of making omeprazole as referred to in these references, salts thereof, enantiomers thereof, and salts of the enantiomers, as well as formulations which may include these compounds, all rely on the chemical structure of omeprazole being accurately determined and the referenced compound or compounds being consistently prepared using the referenced techniques. More specifically, a methoxy group on the benzimidazole ring has been explicitly stated in the literature to be present at the 5-position, in omeprazole, a racemic mixture, and an optically pure isomer of omeprazole designated as **esomeprazole** or **s-omeprazole**. Applicants have now unexpectedly discovered the complexity of omeprazole and the relative bioactivity of each of its previously undiscovered and undisclosed attributes. More specifically, Applicants have confirmed that the methods of the prior art do not yield a single compound having the methoxy group in the 5-position on the benzimidazole ring as previously taught, nor do all of the methods of

the prior art yield consistent results. In fact, omeprazole as conventionally referred to as a bulk drug substance (in its solid state) has been discovered to be present in the form of two pharmaceutically active compounds having the methoxy group on the benzimidazole ring at the 6- and 5-positions. Additionally, Applicants have discovered the presence of a second chiral location at the pyridine ring plane in each of the two compounds such that each compound has two positional isomers and four diastereomers. Therefore, the present invention provides these individual compounds, along with any salts, hydrates, solvates, combinations thereof, and polymorphs thereof, compositions of the above, and methods of making the same that are not taught or suggested by the prior art, pharmaceutical formulations of the compounds, compositions, and complexes of the present invention, and methods for using the same.

SUMM [0073] Accordingly, methods of the present invention provide for improved biological activity/efficacy (e.g. inhibition of gastric acid secretions and, thus, treatment of gastric acid disturbances in mammals, including humans) of pharmaceutically active compounds omeprazole and **esomeprazole**, as presently known in the art, comprising administering to such mammals in need of treatment a non-toxic, therapeutically effective amount of any composition of the present invention comprising compounds or compositions of the present invention having individual diastereomers comprising S.sub.xa--R.sub.4q; S.sub.xa--R.sub.4z; S.sub.xb--R.sub.4q; or S.sub.xb--R.sub.4z, or one or more pharmaceutically acceptable salts, solvates, hydrates, or combinations thereof. Also provided are such methods wherein said compounds or complexes of the present invention having said selected individual diastereomer pair essentially free of compounds of the present invention having diastereomer pairs other than said selected individual diastereomers. A preferred diastereomer is S.sub.xa--R.sub.4q, and an especially preferred diastereomer is S.sub.xa--R.sub.4z.

SUMM [0081] In another aspect, the invention also provides compositions of active pharmaceutical ingredient ("API") comprising any of the compounds, compositions, or complexes of the present invention, each of which may be present in crystalline form, in part or in whole. Advantageously, each such compositions and/or complexes comprising compounds represented by formula (Ia) may also include any one or more of the specific compounds represented by formulae (Iai), (Iaii), (Iaiii), and (Iaiv), or pharmaceutically acceptable salts, solvates, hydrates, polymorphs, or combinations thereof, whether in crystalline form, **amorphous** form, or a combination thereof. Each can be used as the bases for any such API composition.

SUMM [0143] Any of such composition embodiments comprising any of the compounds represented by formulae (Ia) and (Ib), individual species of compounds (Iai)-(Ibi), (Iaii)-(Ibii), (Iaiii)-(Ibiii), and (Iaiv)-(Ibiv), diastereromers thereof, or one or more pharmaceutically acceptable salts, solvates, hydrates, or combinations thereof, may be present in crystalline form, **amorphous** form, or combinations thereof.

SUMM [0144] The invention also provides compositions of active pharmaceutical ingredient ("API") comprising any of the above composition embodiments. Advantageously, any of the compositions comprising compounds represented by formulae (Ia) and (Ib) may also comprise any of the specific compositions represented by formulae (Iai)-(Ibi); (Iaii)-(Ibii); (Iaiii)-(Ibiii); and (Iaiv)-(Ibiv) or one or more pharmaceutically acceptable salts, solvates, hydrates, polymorphs, or combinations thereof, whether in crystalline form, **amorphous** form, or a combination thereof, can be used in any such API compositions.

SUMM [0147] Additionally, when using such processes represented in the prior art, negligible or trace amounts of previously unknown compounds are formed as described herein. For example, in the preparation of such composition as referenced in the immediately preceding paragraph, compounds having the previously unknown diastereomers S.sub.xa--R.sub.4q and S.sub.xb--R.sub.4z are formed with varying and inconsistent ratios of compounds represented by formulae (Ia) and (Ib). Also formed in trace quantities, and typically in **amorphous** form, are compounds represented by formulae (Ia) and (Ib) having the previously unknown diastereomers S.sub.xa--R.sub.4z and S.sub.xb--R.sub.4q.

SUMM [0149] Accordingly, the processes taught in the prior art for the preparation of "omeprazole"as well as "**esomeprazole**" (the intended S-isomer of "omeprazole") provide quantities of previously unknown and unrecognized compounds having pharmaceutical activity, or that are used as intermediates in the preparation of pharmaceutically active compounds of the present invention, or that are used as prodrugs that convert to the active metabolite in vivo. Furthermore, many such processes do not invariably provide the same result when conducted as taught in the prior art.

SUMM [0176] By employing the above method(s) of obtaining the compound represented by formula (Ia) in solid state, one obtains the (-) and (+) enantiomers as a racemic mixture, with these enantiomers including various amounts of diastereomers as set forth herein. In one embodiment, Applicants have discovered that the (-) and (+) enantiomers may be predominantly present as the S.sub.xa--R.sub.4q and S.sub.xb--R.sub.4z diastereomers respectively. Although not intending to be bound by theory, in this embodiment, the two molecules (i.e., compounds of formulae (Ia) and (Ib)) co-crystallize in a centric space group in which the molecules are related to each other through a center of inversion and linked by hydrogen bonding from the amine hydrogens to the sulfoxide oxygens. The R.sub.4 methoxy methyl is directed towards the center of the bridged complex. Examination of the contact distances in the region where the other methoxy-methyl would presumably reside demonstrates that there is not adequate space within the lattice for the other diastereomers (S.sub.xa--R.sub.4z and S.sub.xb--R.sub.4q) to co-exist. In this embodiment, the compound represented by formula (Ia) may comprise about 99 percent (w/w) of the S.sub.xb--R.sub.4z and S.sub.xa--R.sub.4q diastereomers and the remaining percentage of other components which may include, for example, the diastereomers S.sub.xa--R.sub.4z and S.sub.xb--R.sub.4q, generally in **amorphous** form.

SUMM [0182] Although not intending to be bound by theory, such compounds of formula (Ia) are believed to be crystalline with little **amorphous** content. However, when grinding is applied to a solid sample comprising the compound of formula (Ia), and in a preferred embodiment the compounds of formulae (Ia) and (Ib), an increase in the **amorphous** character of the sample is believed to result along with an increase in the amount of compound of formula (Ib). Again, not intending to be bound by theory, it is believed that the sample undergoes a solid state transformation and "recrystallizes" or transforms over a relatively short period of time from the more **amorphous** state to a more crystalline state subsequent to grinding. Nonetheless, it is believed that by performing multiple grinding steps in sequence, (i.e., grinding followed by relaxation followed by grinding) one may obtain a solid sample that becomes more **amorphous** in character and hence comprises a greater amount of the compound of the formula (Ib) as opposed to a sample that has experienced a lesser amount of grinding.

SUMM [0184] The structure of the compound of formula (Ib) can be confirmed by solid state techniques such as, for example, X-ray powder diffraction patterns, Raman, FTIR, solid state NMR, and thermal analysis, of the ground material and the unground material. For example, comparison of the two powder patterns showed distinct decreases in intensity, broadening of the peaks, and an increase in the **amorphous** nature for the ground material. The ground material showed a powder pattern that is more consistent with the proposed more **amorphous** nature of the compound of formula (Ib), e.g., 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

SUMM [0301] The following examples are intended to illustrate the invention, and are not to be construed as limiting the scope of the invention. For the purposes of the examples, the phrase "(5)6-methoxy 2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methylsulfinyl]-1H-benzimidazole" refers to a combination of, preferably a co-crystallized mixture, (with or without an amount of **amorphous** compounds), of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole and 6-methoxy-2-[[(4methoxy-3,5dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole, each as determined and referenced herein.

L2 ANSWER 22 OF 42 USPATFULL on STN

ACCESSION NUMBER:	2003:318198 USPATFULL		
TITLE:	Particulate materials		
INVENTOR(S):	Kordikowski, Andreas, Hellifield, UNITED KINGDOM Walker, Stephen Ernest, Baildon, UNITED KINGDOM York, Peter, Ilkley, UNITED KINGDOM		

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2003223939	A1	20031204	
APPLICATION INFO.:	US 2003-413457	A1	20030414	(10)

	NUMBER	DATE
PRIORITY INFORMATION:	GB 2002-8742	20020417
	GB 2002-9402	20020423

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	NEKTAR THERAPEUTICS, 150 INDUSTRIAL ROAD, SAN CARLOS, CA, 94070
NUMBER OF CLAIMS:	44
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	7 Drawing Page(s)
LINE COUNT:	2015

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to active substances in particulate form, to methods for preparing them, to formulations containing them and to uses of such substances and formulations. A preferred embodiment is directed to particulate suspensions having improved flocculation behaviour in a suspension vehicle, such as a hydrofluoroalkane propellant used in metered dose inhalers.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD [0052] The active substances of the invention are preferably in the form of solid (eg, as opposed to hollow, porous (which includes perforated) or at least partially fluid-containing) particles. They are preferably, although not necessarily, in a crystalline or semi-crystalline (as opposed to **amorphous**) form. More preferably they are

crystalline, ideally highly crystalline, since the crystalline form of a material is often more stable in suspension than its **amorphous** or partially crystalline forms which may more readily dissolve in the fluid vehicle, with a risk of re-crystallisation and/or particle growth.

DETD [0053] An active substance according to the invention is thus preferably from 80% to 100% or from 90 to 100%, ideally 100% crystalline. It may therefore contain less than 20% w/w, preferably less than 10% w/w, more preferably less than 5 or 2 or 1 or even 0.5% w/w, most preferably no, detectable **amorphous** phase regions.

DETD [0055] Levels of **amorphous** and crystalline phases, in an active substance according to the invention, may also be assessed by reference to its moisture uptake at any given temperature and humidity, and/or its thermal activity profile, again in known ways.

DETD [0058] The active substance is preferably in a substantially (eg, 95% w/w or greater, preferably 98% or 99% w/w or 99.5% w/w or greater) pure form. It preferably contains low levels of residual solvent, for example less than 500 ppm, more preferably less than 200 ppm, most preferably less than 150 or 100 ppm residual solvent, by which is meant solvent(s) which were present at the point of particle formation. Still more preferably the substance contains no detectable residual solvent, or at least only levels below the relevant quantification limit(s). It is believed that lower residual solvent levels help to stabilise the particles in fluid suspensions, in particular in the presence of moisture, reducing the tendency for **amorphous** phase regions to re-crystallise and hence for particle growth and agglomeration.

DETD [0082] A typical aerosol canister, for example as used in a metered dose inhaler, can often allow the ingress of atmospheric moisture through its delivery mechanism during medium to long term storage. This moisture can reduce the stability of the suspension inside the canister. The active substances of the present invention can be significantly more stable than for instance their micronised equivalents under such storage conditions, being less susceptible to particle growth and agglomeration even in the presence of moisture. It has been found that even **amorphous** phase active substances according to the invention can be relatively stable under such conditions, despite the fact that moisture would normally be expected to induce re-crystallisation.

DETD [0096] In certain cases, an active substance according to the present invention may be a pharmaceutically active substance or a pharmaceutically acceptable excipient (preferably a substance suitable for and/or intended for delivery by inhalation) other than salmeterol xinafoate (alone or coformulated with hydroxypropyl cellulose); a-lactose monohydrate; R-TEM P-lactamase; maltose; trehalose; sucrose; budesonide; salbutamol sulphate; nicotinic acid; paracetamol (alone or coformulated with salmeterol xinafoate, L-poly(lactic acid), ethyl cellulose (EC), hydroxypropyl methyl cellulose (HPMC) or poly vinyl pyrrolidone (PVP)); ibuprofen; ketoprofen (alone or coformulated with EC, HPMC or PVP); salicylic acid; either indomethacin, carbamazepine, theophylline, ascorbic acid or a COX-2 selective inhibitor coformulated with EC, HPMC or PVP; quinine sulphate coformulated with EC; fluticasone propionate; omeprazole magnesium tetrahydrate; (**S**)-**omeprazole** magnesium trihydrate; formoterol fumarate dihydrate; felodipine; candesartan cilexetil; lysozyme (alone or coformulated with sodium taurocholate); albumin; insulin (alone or coformulated with sodium taurochlorate); terbutaline sulphate; fenoterol hydrobromide and/or ipratropium bromide.

DETD [0188] Sample B precipitated in the form of small plate-like crystals, sample A was **amorphous**.

DETD [0210] It is believed that the high crystallinity of the DHE of the invention contributes to its improved stability in aerosol formulations. **Amorphous** phase regions have a greater tendency to dissolve in a propellant fluid over time, particularly if (as often happens) atmospheric moisture enters the aerosol canister through the valve

mechanism. Following this dissolution, the active substance can then re-crystallise around the still suspended particles, leading to particle growth and/or aggregation and a resultant change in the MMAD as well as in the ultimate aerosol performance. The DHE formulations of the invention appear to have a high degree of stability in this respect, even under conditions representing extended storage periods.

DETD [0211] **Amorphous** and crystalline bromocriptine mesylate samples were prepared as described in Example 8a. Again sample A was **amorphous** and sample B highly crystalline.

DETD [0220] Again, the data for formulations 12A and 12B show good uniformity in dose content over the test period, in particular compared to formulation 12C containing the micronised drug. This indicates good suspension stability for the formulations according to the invention. Even where the active substance is present in the **amorphous** phase, it appears to have extremely good suspension stability in HFA 227ea, which in turn indicates improved stability against re-crystallisation--this is thought to be due to increased purity, and in particular to reduced residual solvent levels, when an active substance is prepared in accordance with the invention as opposed to by a conventional route such as crystallisation followed by micronisation.

L2 ANSWER 23 OF 42 USPATFULL on STN

ACCESSION NUMBER: 2003:309089 USPATFULL

TITLE: Granulated pharmaceutical formulations and methods for making the same

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	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6653329	B1	20031125
APPLICATION INFO.:	US 2003-439865		20030516 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2002-189659, filed on 3 Jul 2002 Continuation of Ser. No. US 2002-57659, filed on 25 Jan 2002, now patented, Pat. No. US 6444689 Continuation of Ser. No. US 2000-645145, filed on 24 Aug 2000, now patented, Pat. No. US 6369087 Continuation-in-part of Ser. No. US 2000-519976, filed on 7 Mar 2000, now patented, Pat. No. US 6262085

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-150878P	19990826 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Reamer, James H
LEGAL REPRESENTATIVE: Myers Bigel Sibley & Sajovec, PA
NUMBER OF CLAIMS: 45
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 0 Drawing Figure(s); 0 Drawing Page(s)
LINE COUNT: 3994
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compounds represented by formula (Ia) are disclosed by the invention, along with compositions and complexes thereof, optionally in combination

with compounds of formula (Ib). Pharmaceutical formulations and methods of making and using such compounds are also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM The teachings regarding the methods of making omeprazole as referred to in these references, salts thereof, enantiomers thereof, and salts of the enantiomers, as well as formulations which may include these compounds, all rely on the chemical structure of omeprazole being accurately determined and the referenced compound or compounds being consistently prepared using the referenced techniques. More specifically, a methoxy group on the benzimidazole ring has been explicitly stated in the literature to be present at the 5-position, in omeprazole, a racemic mixture, and an optically pure isomer of omeprazole designated as **esomeprazole** or **s-omeprazole**. Applicants have now unexpectedly discovered the complexity of omeprazole and the relative bioactivity of each of its previously undiscovered and undisclosed attributes. More specifically, Applicants have confirmed that the methods of the prior art do not yield a single compound having the methoxy group in the 5-position on the benzimidazole ring as previously taught, nor do all of the methods of the prior art yield consistent results. In fact, omeprazole as conventionally referred to as a bulk drug substance (in its solid state) has been discovered to be present in the form of two pharmaceutically active compounds having the methoxy group on the benzimidazole ring at the 6- and 5-positions. Additionally, Applicants have discovered the presence of a second chiral location at the pyridine ring plane in each of the two compounds such that each compound has two positional isomers and four diastereomers. Therefore, the present invention provides these individual compounds, along with any salts, hydrates, solvates, combinations thereof, and polymorphs thereof, compositions of the above, and methods of making the same that are not taught or suggested by the prior art, pharmaceutical formulations of the compounds, compositions, and complexes of the present invention, and methods for using the same.

SUMM Accordingly, methods of the present invention provide for improved biological activity/efficacy (e.g. inhibition of gastric acid secretions and, thus, treatment of gastric acid disturbances in mammals, including humans) of pharmaceutically active compounds omeprazole and **esomeprazole**, as presently known in the art, comprising administering to such mammals in need of treatment a non-toxic, therapeutically effective amount of any composition of the present invention comprising compounds or compositions of the present invention having individual diastereomers comprising S.sub.xa--R.sub.4q; S.sub.xa--R.sub.4z; S.sub.xb--R.sub.4q; or S.sub.xb--R.sub.4z, or one or more pharmaceutically acceptable salts, solvates, hydrates, or combinations thereof. Also provided are such methods wherein said compounds or complexes of the present invention having said selected individual diastereomer pair essentially free of compounds of the present invention having diastereomer pairs other than said selected individual diastereomers. A preferred diastereomer is S.sub.xa--R.sub.4q, and an especially preferred diastereomer is S.sub.xa R.sub.4z.

SUMM In another aspect, the invention also provides compositions of active pharmaceutical ingredient ("API") comprising any of the compounds, compositions, or complexes of the present invention, each of which may be present in crystalline form, in part or in whole. Advantageously, each such compositions and/or complexes comprising compounds represented by formula (Ia) may also include any one or more of the specific compounds represented by formulae (Iaid, (Iaii), (Iaiii), and (Iaiv), or pharmaceutically acceptable salts, solvates, hydrates, polymorphs, or combinations thereof, whether in crystalline form, **amorphous**

forms or a combination thereof. Each can be used as the bases for any such API composition.

SUMM Any of such composition embodiments comprising any of the compounds represented by formulae (Ia) and (Ib), individual species of compounds (Iai)-(Ibi), (Iaii)-(Ibii), (Iaiii)-(Ibiii), and (Iaiv)-(Ibiv), diastereromers thereof, or one or more pharmaceutically acceptable salts, solvates, hydrates, or combinations thereof, may be present in crystalline form, **amorphous** form, or combinations thereof.

SUMM The invention also provides compositions of active pharmaceutical ingredient ("API") comprising any of the above composition embodiments. Advantageously, any of the compositions comprising compounds represented by formulae (Ia) and (Ib) may also comprise any of the specific compositions represented by formulae (Iai)-(Ibi); (Iaii)-(Ibii); (Iaiii)-(Ibiii); and (Iaiv)-(Ibiv) or one or more pharmaceutically acceptable salts, solvates, hydrates, polymorphs, or combinations thereof, whether in crystalline form, **amorphous** form, or a combination thereof, can be used in any such API compositions.

SUMM Additionally when using such processes represented in the prior art, negligible or trace amounts of previously unknown compounds are formed as described herein. For example, in the preparation of such composition as referenced in the immediately preceding paragraph; compounds having the previously unknown diastereomers S.sub.xa--R.sub.4q and S.sub.xb--R.sub.4z are formed with varying and inconsistent ratios of compounds represented by formulae (Ia) and (Ib). Also formed in trace quantities, and typically in **amorphous** form, are compounds represented by formulae (Ia) and (Ib) having the previously unknown diastereomers S.sub.xa--R.sub.4z and S.sub.xb--R.sub.4q.

SUMM Accordingly, the processes taught in the prior art for the preparation of "omeprazole" as well as "**esomeprazole**" (the intended S-isomer of "omeprazole") provide quantities of previously unknown and unrecognized compounds having pharmaceutical activity, or that are used as intermediates in the preparation of pharmaceutically active compounds of the present invention, or that are used as prodrugs that convert to the active metabolite in vivo. Furthermore, many such processes do not invariably provide the same result when conducted as taught in the prior art

SUMM Although not intending to be bound by theory, such compounds of formula (Ia) are believed to be crystalline with little **amorphous** content. However, when grinding is applied to a solid sample comprising the compound of formula (Ia), and in a preferred embodiment the compounds of formulae (Ia) and (Ib), an increase in the **amorphous** character of the sample is believed to result along with an increase in the amount of compound of formula (Ib). Again, not intending to be bound by theory, it is believed that the sample undergoes a solid state transformation and "recrystallizes" or transforms over a relatively short period of time from the more **amorphous** state to a more crystalline state subsequent to grinding. Nonetheless, it is believed that by performing multiple grinding steps in sequence, (i.e. grinding followed by relaxation followed by grinding) one may obtain a solid sample that becomes more **amorphous** in character and hence comprises a greater amount of the compound of the formula (Ib) as opposed to a sample that has experienced a lesser amount of grinding.

SUMM The structure of the compound of formula (Ib) can be confirmed by solid state techniques such as, for example, X-ray powder diffraction patterns, Raman, FTIR, solid state NMR, and thermal analysis, of the

ground material and the unground material. For example, comparison of the two powder patterns showed distinct decreases in intensity, broadening of the peaks, and an increase in the **amorphous** nature for the ground material. The ground material showed a powder pattern that is more consistent with the proposed more **amorphous** nature of the compound of formula (Ib), e.g., 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

SUMM The following examples are intended to illustrate the invention, and are not to be construed as limiting the scope of the invention. For the purposes of the examples, the phrase "(5)6-methoxy 2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole" refers to a combination of, preferably a co-crystallized mixture, (with or without an amount of **amorphous** compounds), of 5-methoxy-2-[[(4-methoxy-3-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole and 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole, each as determined and referenced herein.

L2 ANSWER 24 OF 42 USPATFULL on STN
ACCESSION NUMBER: 2003:257302 USPATFULL
TITLE: Solid carriers for improved delivery of active ingredients in pharmaceutical compositions
INVENTOR(S): Patel, Mahesh V., Salt Lake City, UT, UNITED STATES
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	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003180352	A1	20030925
APPLICATION INFO.:	US 2002-159601	A1	20020530 (10)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2001-800593, filed on 6 Mar 2001, PENDING Division of Ser. No. US 1999-447690, filed on 23 Nov 1999, GRANTED, Pat. No. US 6248363
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: REED & ASSOCIATES, 800 MENLO AVENUE, SUITE 210, MENLO PARK, CA, 94025
NUMBER OF CLAIMS: 55
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 4 Drawing Page(s)
LINE COUNT: 4625
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides solid pharmaceutical compositions for improved delivery of a wide variety of active ingredients contained therein or separately administered. In one embodiment, the solid pharmaceutical composition includes a solid carrier, the solid carrier including a substrate and an encapsulation coat on the substrate. The encapsulation coat can include different combinations of active ingredients, hydrophilic surfactant, lipophilic surfactants and triglycerides, and solubilizers. In another embodiment, the solid pharmaceutical composition includes a solid carrier, the solid carrier being formed of different combinations of active ingredients, hydrophilic surfactants, lipophilic surfactants and triglycerides, and solubilizers. The compositions of the present invention can be used for improved delivery of active ingredients.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD [0058] gastrointestinal agents, such as alosetron, basalazide, bisacodyl, budesonide, cilansetron, cimetidine, cisapride, diphenoxylate, domperidone, **esomeprazole**, famotidine, granisetron, lafutidine, lansoprazole, leminoprazole, loperamide,

merropenum, mesalazine, mesalamine, nitisonone, nizatidine, olsalazine, omeprazole, ondansetron, pantoprazole, palonosetron, pariprazole, rabeprazole sodium, ransoprazole, ranitidine, risperidone, sulphasalazine, and tegaserod;

DETD [0106] Specific, non-limiting examples of suitable hydrophobic active ingredients are: acetretin, acetyl coenzyme Q, albendazole, albuterol, aminoglutethimide, amiodarone, amlodipine, amphetamine, amphotericin B, atorvastatin, atovaquone, azithromycin, baclofen, beclomethasone, benezepril, benzonatate, betamethasone, bicalutanide, budesonide, bupropion, busulfan, butenafine, calcifediol, calcipotriene, calcitriol, camptothecin, candesartan, capsaicin, carbamezepine, carotenes, celecoxib, cerivastatin, cetirizine, chlorpheniramine, cholecalciferol, cilostazol, cimetidine, cinnarizine, ciprofloxacin, cisapride, clarithromycin, clemastine, clomiphene, clomipramine, clopidogrel, codeine, coenzyme Q10, cyclobenzaprine, cyclosporin, danazol, dantrolene, dexchlorpheniramine, diclofenac, dicoumarol, digoxin, dehydroepiandrosterone, dihydroergotamine, dihydrotachysterol, dirithromycin, donezepil, efavirenz, eposartan, ergocalciferol, ergotamine, essential fatty acid sources, **esomeprazole**, estradiol, etodolac, etoposide, famotidine, fenofibrate, fentanyl, fexofenadine, finasteride, fluconazole, flurbiprofen, fluvastatin, fosphenytoin, frovatriptan, furazolidone, gabapentin, gemfibrozil, glibenclamide, glipizide, glyburide, glimepiride, griseofulvin, halofantrine, ibuprofen, irbesartan, irinotecan, isosorbide dinitrate, isotretinoin, itraconazole, ivermectin, ketoconazole, ketorolac, lamotrigine, lansoprazole, leflunomide, lisinopril, loperamide, loratadine, lovastatin, L-thryroxine, lutein, lycopene, medroxyprogesterone, mifepristone, mefloquine, megestrol acetate, methadone, methoxsalen, metronidazole, miconazole, midazolam, miglitol, minoxidil, mitoxantrone, montelukast, nabumetone, nalbuphine, naratriptan, nelfinavir, nifedipine, nisoldipine, nilutanide, nitrofurantoin, nizatidine, omeprazole, oprevelkin, oxaprozin, paclitaxel, pantoprazole, paracalcitol, paroxetine, pentazocine, pioglitazone, pizofetin, pravastatin, prednisolone, probucol, progesterone, pseudoephedrine, pyridostigmine, rabeprazole, raloxifene, repaglinide, rifabutine, rifapentine, rimexolone, ritanovir, rizatriptan, rofecoxib, rosiglitazone, saquinavir, sertraline, sibutramine, sildenafil citrate, simvastatin, sirolimus, spironolactone, sumatriptan, tacrine, tacrolimus, tamoxifen, tamsulosin, targretin, tazarotene, telmisartan, teniposide, terbinafine, terazosin, tetrahydrocannabinol, tiagabine, ticlopidine, tirofibran, tizanidine, topiramate, topotecan, toremifene, tramadol, tretinoin, troglitazone, trovafloxacin, ubidecarenone, valsartan, venlafaxine, verteporfin, vigabatrin, vitamin A, vitamin D, vitamin E, vitamin K, zafirlukast, zileuton, zolmitriptan, zolpidem, and zopiclone. Of course, salts, isomers and derivatives of the above-listed hydrophobic active ingredients may also be used, as well as mixtures thereof.

DETD [0107] Among the above-listed hydrophobic active ingredients, preferred active ingredients include: acetretin, albendazole, albuterol, aminoglutethimide, amiodarone, amlodipine, amphetamine, amphotericin B, atorvastatin, atovaquone, azithromycin, baclofen, benzonatate, bicalutanide, busulfan, butenafine, calcifediol, calcipotriene, calcitriol, camptothecin, capsaicin, carbamezepine, carotenes, celecoxib, cerivastatin, chlorpheniramine, cholecaliferol, cimetidine, cinnarizine, ciprofloxacin, cisapride, cetirizine, clarithromycin, clemastine, clomiphene, codeine, coenzyme Q10, cyclosporin, danazol, dantrolene, dexchlorpheniramine, diclofenac, digoxin, dehydroepiandrosterone, dihydroergotamine, dihydrotachysterol, dirithromycin, donezepil, efavirenz, ergocalciferol, ergotamine, **esomeprazole**, essential fatty acid sources, etodolac, etoposide, famotidine, fenofibrate, fentanyl, fexofenadine, finasteride, fluconazole, flurbiprofen, fluvastatin, fosphenytoin, frovatriptan,

furazolidone, gabapentin, gemfibrozil, glibenclamide, glipizide, glyburide, glimepiride, griseofulvin, halofantrine, ibuprofen, irinotecan, isotretinoin, itraconazole, ivermectin, ketoconazole, ketorolac, lamotrigine, lansoprazole, leflunomide, loperamide, loratadine, lovastatin, L-thryroxine, lutein, lycopene, mifepristone, mefloquine, megestrol acetate, methdone, methoxsalen, metronidazole, miconazole, midazolam, miglitol, mitoxantrone, medroxyprogesterone, montelukast, nabumetone, nalbuphine, naratriptan, nelfinavir, nilutanide, nitrofurantoin, nizatidine, omeprazole, oestradiol, oxaprozin, paclitaxel, pantoprazole, paracalcitol, pentazocine, pioglitazone, pizofetin, pravastatin, probucol, progesterone, pseudoephedrine, pyridostigmine, rabeprazole, raloxifene, rofecoxib, repaglinide, rifabutine, rifapentine, rimexolone, ritanovir, rizatriptan, rosiglitazone, saquinavir, sibutramine, sildenafil citrate, simvastatin, sirolimus, spironolactone, sumatriptan, tacrine, tacrolimus, tamoxifen, tamsulosin, targretin, tazarotene, teniposide, terbinafine, tetrahydrocannabinol, tiagabine, tizanidine, topiramate, topotecan, toremifene, tramadol, tretinoin, troglitazone, trovafloxacin, verteporfin, vigabatrin, vitamin A, vitamin D, vitamin E, vitamin K, zafirlukast, zileuton, ziprasidone, zolmitriptan, zolpidem, zopiclone, pharmaceutically acceptable salts, isomers and derivatives thereof, and mixtures thereof.

DETD [0108] Particularly preferred hydrophobic active ingredients include: acetretin, albuterol, aminoglutethimide, amiodarone, amlodipine, amprenavir, atorvastatin, atovaquone, baclofen, benzonatate, bicalutanide, busulfan, calcifediol, calcipotriene, calcitriol, camptothecin, capsaicin, carbamezepine, carotenes, celecoxib, chlorpheniramine, cholecaliferol, cimetidine, cinnarizine, cisapride, cetirizine, clemastine, coenzyme Q10, cyclosporin, danazol, dantrolene, dexchlorpheniramine, diclofenac, dehydroepiandrosterone, dihydroergotamine, dihydrotachysterol, efavirenz, ergocalciferol, ergotamine, **esomeprazole**, essential fatty acid sources, etodolac, etoposide, famotidine, fenofibrate, fexofenadine, finasteride, fluconazole, flurbiprofen, fosphenytoin, frovatriptan, furazolidone, glibenclamide, glipizide, glyburide, glimepiride, ibuprofen, irinotecan, isotretinoin, itraconazole, ivermectin, ketoconazole, ketorolac, lamotrigine, lansoprazole, leflunomide, loperamide, loratadine, lovastatin, L-thryroxine, lutein, lycopene, medroxyprogesterone, mifepristone, megestrol acetate, methoxsalen, metronidazole, miconazole, miglitol, mitoxantrone, montelukast, nabumetone, naratriptan, nelfinavir, nilutanide, nitrofurantoin, nizatidine, omeprazole, oestradiol, oxaprozin, paclitaxel, pantoprazole, paracalcitol, pioglitazone, pizofetin, pranlukast, probucol, progesterone, pseudoephedrine, rabeprazole, raloxifene, rofecoxib, repaglinide, rifabutine, rifapentine, rimexolone, ritanovir, rizatriptan, rosiglitazone, saquinavir, sildenafil citrate, simvastatin, sirolimus, tacrolimus, tamoxifen, tamsulosin, targretin, tazarotene, teniposide, terbenafine, tetrahydrocannabinol, tiagabine, tizanidine, topiramate, topotecan, toremifene, tramadol, tretinoin, troglitazone, trovafloxacin, ubidecarenone, vigabatrin, vitamin A, vitamin D, vitamin E, vitamin K, zafirlukast, zileuton, ziprasidone, zolmitriptan, pharmaceutically acceptable salts, isomers and derivatives thereof, and mixtures thereof.

DETD [0115] A preferred class of acid-labile active ingredients are benzimidazoles, particularly those useful as proton pump inhibitors such as **esomeprazole**, lansoprazole, omeprazole, pantoprazole, rabeprazole, pharmaceutically acceptable salts, isomers and derivatives thereof, and combinations thereof; and most preferably lansoprazole, pantoprazole, rabeprazole, pharmaceutically acceptable salts, isomers and derivatives thereof, and combinations thereof. Exemplary salts include the sodium, potassium, calcium and magnesium salts of the active ingredient. It is understood that reference made to an active ingredient, such as lansoprazole is intended to mean the active per se,

as well as pharmaceutically acceptable salts, isomers and derivatives thereof.

DETD [0315] In another embodiment of the invention, the active agent is in the form of a plurality of solid particles, which may associate to form one or more larger dosage units such as a granule, pellet, bead or tablet, suspended in the vehicle. The particles may be single phase, or comprised of two or more phases. When the solid particles are wholly comprised of the active agent, the particulate phase can be **amorphous** or in a high energy state, i.e., a metastable crystalline phase or a stable crystalline phase (wherein the crystalline state may include any of various polymorphs or solvates), or it may be a mixture of at least one **amorphous** phase and at least one crystalline phase. For example, in a preferred embodiment, the active ingredient is present in its crystalline form. This is of particular interest for compounds such as lansoprazole, whose crystalline form is not readily soluble in water.

DETD [0316] When the particles include one or more excipients, additives, or the like, the particulate material can be **amorphous**, crystalline, in the form of a solid solution with the excipient(s) and/or additive(s), or a mixture of two or more of these phases. The solid particles may contain a core comprised of the active agent, an excipient, or mixtures thereof, and may optionally be further coated with at least one layer of the active agent, the excipient, or mixtures thereof. The solid particles may be core-free, in the form of a powder or a plurality of granules, pellets, and/or beads, or combinations thereof.

DETD [0381] The active ingredient can be a proton pump inhibitor such as lansoprazole, omeprazole, **esomeprazole**, pantoprazole, rabeprazole, as well as a pharmaceutically acceptable salt, isomer or derivative thereof.

DETD [0388] Exemplary dosing regiments for **esomeprazole** include 20-40 mg/day for healing and maintenance of healing of erosive esophagitis and for treatment of symptomatic gastroesophageal reflux disease.

DETD [0389] Exemplary combined dosing regiments for **esomeprazole**, amoxicillin, and clarithromycin for H. pylori eradication to reduce the risk of duodenal ulcer recurrence, is a once daily dose of 40 mg **esomeprazole** and twice daily dose of 1000 mg amoxicillin, and 500 mg clarithromycin.

CLM What is claimed is:

37. A pharmaceutical composition in the form of a solid carrier comprising an admixture of: a) a therapeutically effective amount of an active ingredient selected from the group consisting of **esomeprazole**, pantoprazole, rabeprazole, and pharmaceutically acceptable salts, isomers and derivatives thereof; and b) at least one excipient selected from the group consisting of: i) a hydrophilic surfactant; ii) at least one lipophilic additive selected from the group consisting of lipophilic surfactants, triglycerides, and combinations thereof; and iii) a solubilizer.

49. A method of administering an active ingredient selected from the group consisting of **esomeprazole**, pantoprazole, rabeprazole, and pharmaceutically acceptable salts, isomers and derivatives thereof, to an individual comprising orally administering to the individual a dosage form of the pharmaceutical composition of claim 37.

51. A method of improving the oral bioavailability of an active ingredient selected from the group consisting of **esomeprazole**, pantoprazole, rabeprazole, and pharmaceutically acceptable salts, isomers and derivatives thereof, in mammals under fed condition, comprising orally administering to the mammal a dosage form of the pharmaceutical composition of claim 37.

53. A method of improving the in vivo or ex vivo stability of an active ingredient at a pH within the range of about 1-6.8, wherein the active agent is selected from the group consisting of **esomeprazole**, pantoprazole, rabeprazole, and pharmaceutically acceptable salts, isomers and derivatives thereof, comprising formulating the active ingredient in a pharmaceutical composition comprising at least one excipient selected from the group consisting of: a) a hydrophilic surfactant; b) at least one lipophilic additive selected from the group consisting of lipophilic surfactants, triglycerides, and combinations thereof; and c) a solubilizer; and optionally providing the pharmaceutical composition with a seal coat or an enteric coat.

54. A method of improving the stability of an active ingredient during storage, wherein the active ingredient selected from the group consisting of **esomeprazole**, pantoprazole, rabeprazole, and pharmaceutically acceptable salts, isomers and derivatives thereof, comprising formulating the active ingredient in pharmaceutical composition comprising at least one excipient selected from the group consisting of: a) a hydrophilic surfactant; b) at least one lipophilic additive selected from the group consisting of lipophilic surfactants, triglycerides, and combinations thereof; and c) a solubilizer; and optionally providing the pharmaceutical composition with a seal coat, wherein at least one of the lipophilic additive or seal coat reduces the permeation of moisture to the active ingredient.

L2 ANSWER 25 OF 42 USPATFULL on STN

ACCESSION NUMBER:	2003:196965 USPATFULL		
TITLE:	Method of producing drug particles		
INVENTOR(S):	Boissier, Catherine, Goteborg, SWEDEN Juppo, Anne Mari, Molndal, SWEDEN		
PATENT ASSIGNEE(S):	AstraZeneca AB, Sodertalje, SWEDEN (non-U.S. corporation)		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6596315	B1	20030722
	WO 2000030612		20000602
APPLICATION INFO.:	US 2000-486688		20000301 (9)
	WO 1999-SE2152		19991122
	NUMBER		DATE
PRIORITY INFORMATION:	SE 1998-4003		19981123
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	GRANTED		
PRIMARY EXAMINER:	Page, Thurman K.		
ASSISTANT EXAMINER:	Joynes, Robert M.		
LEGAL REPRESENTATIVE:	White & Case LLP		
NUMBER OF CLAIMS:	7		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	0 Drawing Figure(s); 0 Drawing Page(s)		
LINE COUNT:	416		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method of preparing drug particles of a substance which are susceptible to degradation by the use of a fluid gas technique.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM The substances can be, but are not limited to pharmaceutically active substances such as: hydrates of omeprazole, omeprazole Mg, omeprazole Na (S)-**omeprazole**, (S)-**omeprazole** K

(dimethanolsolvate), (S)-**omeprazole** Mg (S
)-**omeprazole** Na, formoterol funarate etc.

DETD Omeprazole magnesium, tetrahydrate (Astra AB, Sweden), (S)-**omeprazole** magnesium, trihydrate (Astra AB, Sweden), formoterol fumarate, dihydrate (Astra AB, Sweden) were used as active substances. Ethanol (99.5%), methanol (99.8%), ammonia (33%), acetone (99.5%) and water were used as solvents. Carbon dioxide (food grade) and ethane (99.0%) were used as antisolvents (AGA gas AB).

DETD (S)-**omeprazole** Magnesium, Trihydrate

DETD (S)-**omeprazole** magnesium was dissolved in ethanol, in an ultrasonic bath. After dissolution, water was slowly added to the solution. One composition of the **s-omeprazole** magnesium solution was used in the experiments (Table 3).

DETD

TABLE 3

Compositions of the (S)-**omeprazole** magnesium solution.

Composition no.	Solution experiments	Ethanol Concentration (99.5%) (w/v %)	Water (v %)	(v %)
2-1	2-1a	1.0	97.0	3.0
2-1	2-1b	1.0	97.0	3.0

DETD The particles made from a solution, using ethanol and water as solvents, were crystallised as (S)-**omeprazole** magnesium hydrate, when ethane was used as antisolvent (PXRD, FT-Raman). Sample 2-1b was found to contain about 3.4 moles of hard bound water (TGA). The pattern of weight loss suggests that the sample is crystalline. The degradation products in 2-1b were 0.3 area % (HPLC).

DETD The particles formed, using carbon dioxide as antisolvent were **amorphous.** The analysis shows no crystalline content in sample 2-1a (PXRD, FT-Raman). The pattern of weight of loss suggests that the sample is **amorphous** (TGA). The degradation products were 2.1 area % in 2-1a (HPLC).

DETD When using carbon dioxide as antisolvent, the produced particles in experiment 3-1a contained **amorphous** formoterol fumarate (composition 3-1 in Table 5). Experiment 3-2a resulted in a mixture of formoterol fumarate dihydrate and formoterol fumarate anhydrate B (composition 3-2 in Table 5) (pXRD, TGA). The degradation products were 0.26 weight % in 3-1a and 0.22 weight % in 3-2a (HPLC).

CLM What is claimed is:

3. The method according to claim 1 wherein the acid-labile substance is a hydrate of (S)-**omeprazole**, or its magnesium, sodium or potassium salt.

L2 ANSWER 26 OF 42 USPATFULL on STN

ACCESSION NUMBER: 2003:141003 USPATFULL

TITLE: Alkoxy substituted benzimidazole compounds, pharmaceutical preparations containing the same, and methods of using the same

INVENTOR(S): Whittle, Robert R., Wilmington, NC, UNITED STATES
Sancillio, Frederick D., Wilmington, NC, UNITED STATES
Stowell, Grayson Walker, Wilmington, NC, UNITED STATES
Jenkins, Douglas John, Wilmington, NC, UNITED STATES
Whittall, Linda B., Wilmington, NC, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003096845	A1	20030522
	US 6667321	B2	20031223

10/690,897

APPLICATION INFO.: US 2002-189659 A1 20020703 (10)
RELATED APPLN. INFO.: Continuation of Ser. No. US 2002-57659, filed on 25 Jan 2002, GRANTED, Pat. No. US 6444689 Continuation of Ser. No. US 2000-645145, filed on 24 Aug 2000, GRANTED, Pat. No. US 6369087 Continuation-in-part of Ser. No. US 2000-519976, filed on 7 Mar 2000, GRANTED, Pat. No. US 6262085

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-150878P	19990826 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: MYERS BIGEL SIBLEY & SAJOVEC, PO BOX 37428, RALEIGH, NC, 27627
NUMBER OF CLAIMS: 64
EXEMPLARY CLAIM: 1
LINE COUNT: 4128
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Compounds represented by formula (Ia) are disclosed by the invention, along with compositions and complexes thereof, optionally in combination with compounds of formula (Ib). Pharmaceutical formulations and methods of making and using such compounds are also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM [0010] The teachings regarding the methods of making omeprazole as referred to in these references, salts thereof, enantiomers thereof, and salts of the enantiomers, as well as formulations which may include these compounds, all rely on the chemical structure of omeprazole being accurately determined and the referenced compound or compounds being consistently prepared using the referenced techniques. More specifically, a methoxy group on the benzimidazole ring has been explicitly stated in the literature to be present at the 5-position, in omeprazole, a racemic mixture, and an optically pure isomer of omeprazole designated as **esomeprazole** or **s-omeprazole**. Applicants have now unexpectedly discovered the complexity of omeprazole and the relative bioactivity of each of its previously undiscovered and undisclosed attributes. More specifically, Applicants have confirmed that the methods of the prior art do not yield a single compound having the methoxy group in the 5-position on the benzimidazole ring as previously taught, nor do all of the methods of the prior art yield consistent results. In fact, omeprazole as conventionally referred to as a bulk drug substance (in its solid state) has been discovered to be present in the form of two pharmaceutically active compounds having the methoxy group on the benzimidazole ring at the 6- and 5-positions. Additionally, Applicants have discovered the presence of a second chiral location at the pyridine ring plane in each of the two compounds such that each compound has two positional isomers and four diastereomers. Therefore, the present invention provides these individual compounds, along with any salts, hydrates, solvates, combinations thereof, and polymorphs thereof, compositions of the above, and methods of making the same that are not taught or suggested by the prior art, pharmaceutical formulations of the compounds, compositions, and complexes of the present invention, and methods for using the same.

SUMM [0073] Accordingly, methods of the present invention provide for improved biological activity/efficacy (e.g. inhibition of gastric acid secretions and, thus, treatment of gastric acid disturbances in mammals, including humans) of pharmaceutically active compounds omeprazole and **esomeprazole**, as presently known in the art, comprising administering to such mammals in need of treatment a non-toxic, therapeutically effective amount of any composition of the present

invention comprising compounds or compositions of the present invention having individual diastereomers comprising S.sub.xa-R.sub.4q; S.sub.xa-R.sub.4z; S.sub.xb-R.sub.4q; or S.sub.xb-R.sub.4z, or one or more pharmaceutically acceptable salts, solvates, hydrates, or combinations thereof. Also provided are such methods wherein said compounds or complexes of the present invention having said selected individual diastereomer pair essentially free of compounds of the present invention having diastereomer pairs other than said selected individual diastereomers. A preferred diastereomer is S.sub.xa-R.sub.4q, and an especially preferred diastereomer is S.sub.xa-R.sub.4z.

SUMM [0081] In another aspect, the invention also provides compositions of active pharmaceutical ingredient ("API") comprising any of the compounds, compositions, or complexes of the present invention, each of which may be present in crystalline form, in part or in whole. Advantageously, each such compositions and/or complexes comprising compounds represented by formula (Ia) may also include any one or more of the specific compounds represented by formulae (Iai), (Iaii), (Iaiii), and (Iaiv), or pharmaceutically acceptable salts, solvates, hydrates, polymorphs, or combinations thereof, whether in crystalline form, **amorphous** form, or a combination thereof. Each can be used as the bases for any such API composition.

SUMM [0142] Any of such composition embodiments comprising any of the compounds represented by formulae (Ia) and (Ib), individual species of compounds (Iai)-(Ibi), (Iaii)-(Ibii), (Iaiii)-(Ibiii), and (Iaiv)-(Ibiv), diastereromers thereof, or one or more pharmaceutically acceptable salts, solvates, hydrates, or combinations thereof, may be present in crystalline form, **amorphous** form, or combinations thereof.

SUMM [0143] The invention also provides compositions of active pharmaceutical ingredient ("API") comprising any of the above composition embodiments. Advantageously, any of the compositions comprising compounds represented by formulae (Ia) and (Ib) may also comprise any of the specific compositions represented by formulae (Iai)-(Ibi); (Iaii)-(Ibii); (Iaiii)-(Ibiii); and (Iaiv)-(Ibiv) or one or more pharmaceutically acceptable salts, solvates, hydrates, polymorphs, or combinations thereof, whether in crystalline form, **amorphous** form, or a combination thereof, can be used in any such API compositions.

SUMM [0146] Additionally, when using such processes represented in the prior art, negligible or trace amounts of previously unknown compounds are formed as described herein. For example, in the preparation of such composition as referenced in the immediately preceding paragraph, compounds having the previously unknown diastereomers S.sub.xa-R.sub.4q and S.sub.xb-R.sub.4z are formed with varying and inconsistent ratios of compounds represented by formulae (Ia) and (Ib). Also formed in trace quantities, and typically in **amorphous** form, are compounds represented by formulae (Ia) and (Ib) having the previously unknown diastereomers S.sub.xa-R.sub.4z and S.sub.xb-R.sub.4q.

SUMM [0148] Accordingly, the processes taught in the prior art for the preparation of "omeprazole" as well as "**esomeprazole**" (the intended S-isomer of "omeprazole") provide quantities of previously unknown and unrecognized compounds having pharmaceutical activity, or that are used as intermediates in the preparation of pharmaceutically active compounds of the present invention, or that are used as prodrugs that convert to the active metabolite in vivo. Furthermore, many such processes do not invariably provide the same result when conducted as taught in the prior art.

SUMM [0175] By employing the above method(s) of obtaining the compound represented by formula (Ia) in solid state, one obtains the (-) and (+) enantiomers as a racemic mixture, with these enantiomers including various amounts of diastereomers as set forth herein. In one embodiment, Applicants have discovered that the (-) and (+) enantiomers may be predominantly present as the S.sub.xa-R.sub.4q and S.sub.xb-R.sub.4z diastereomers respectively. Although not intending to be bound by theory, in this embodiment, the two molecules (i.e., compounds of formulae (Ia) and (Ib)) co-crystallize in a centric space group in which the molecules are related to each other through a center of inversion and linked by hydrogen bonding from the amine hydrogens to the sulfoxide oxygens. The R.sub.4 methoxy methyl is directed towards the center of the bridged complex. Examination of the contact distances in the region where the other methoxy methyl would presumably reside demonstrates that there is not adequate space within the lattice for the other diastereomers (S.sub.xa-R.sub.4z and S.sub.xb-R.sub.4q) to co-exist. In this embodiment, the compound represented by formula (Ia) may comprise about 99 percent (w/w) of the S.sub.xb-R.sub.4z and S.sub.xa-R.sub.4q diastereomers and the remaining percentage of other components which may include, for example, the diastereomers S.sub.xa-R.sub.4z and S.sub.xb-R.sub.4q, generally in **amorphous** form.

SUMM [0181] Although not intending to be bound by theory, such compounds of formula (Ia) are believed to be crystalline with little **amorphous** content. However, when grinding is applied to a solid sample comprising the compound of formula (Ia), and in a preferred embodiment the compounds of formulae (Ia) and (Ib), an increase in the **amorphous** character of the sample is believed to result along with an increase in the amount of compound of formula (Ib). Again, not intending to be bound by theory, it is believed that the sample undergoes a solid state transformation and "recrystallizes" or transforms over a relatively short period of time from the more **amorphous** state to a more crystalline state subsequent to grinding. Nonetheless, it is believed that by performing multiple grinding steps in sequence, (i.e., grinding followed by relaxation followed by grinding) one may obtain a solid sample that becomes more **amorphous** in character and hence comprises a greater amount of the compound of the formula (Ib) as opposed to a sample that has experienced a lesser amount of grinding.

SUMM [0183] The structure of the compound of formula (Ib) can be confirmed by solid state techniques such as, for example, X-ray powder diffraction patterns, Raman, FTIR, solid state NMR, and thermal analysis, of the ground material and the unground material. For example, comparison of the two powder patterns showed distinct decreases in intensity, broadening of the peaks, and an increase in the **amorphous** nature for the ground material. The ground material showed a powder pattern that is more consistent with the proposed more **amorphous** nature of the compound of formula (Ib), e.g., 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

SUMM [0301] The following examples are intended to illustrate the invention, and are not to be construed as limiting the scope of the invention. For the purposes of the examples, the phrase "(5)6-methoxy 2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole" refers to a combination of, preferably a co-crystallized mixture, (with or without an amount of **amorphous** compounds), of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole and 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole, each as determined and referenced herein.

L2 ANSWER 27 OF 42 USPATFULL on STN
ACCESSION NUMBER: 2003:112567 USPATFULL
TITLE: Pharmaceutical formulations and systems for improved absorption and multistage release of active agents
INVENTOR(S): Chen, Feng-Jing, Salt Lake City, UT, UNITED STATES
Venkateshwaran, Srinivasan, Salt Lake City, UT, UNITED STATES
Krill, Steven L., Park City, UT, UNITED STATES
Patel, Mahesh V., Salt Lake City, UT, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003077297	A1	20030424
APPLICATION INFO.:	US 2002-74687	A1	20020211 (10)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2001-898553, filed on 2 Jul 2001, PENDING Continuation of Ser. No. US 1999-258654, filed on 26 Feb 1999, GRANTED, Pat. No. US 6294192 Continuation-in-part of Ser. No. US 2001-877541, filed on 8 Jun 2001, PENDING Continuation-in-part of Ser. No. US 1999-345615, filed on 30 Jun 1999, GRANTED, Pat. No. US 6267985 Continuation-in-part of Ser. No. US 2001-800593, filed on 6 Mar 2001, PENDING Division of Ser. No. US 1999-447690, filed on 23 Nov 1999, GRANTED, Pat. No. US 6248363
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: REED & ASSOCIATES, 800 MENLO AVENUE, SUITE 210, MENLO PARK, CA, 94025
NUMBER OF CLAIMS: 145
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 7 Drawing Page(s)
LINE COUNT: 4845
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention pertains to pharmaceutical formulations and systems for delivery of active agents, wherein a first fraction of an active agent is suspended in a vehicle and a second fraction of active agent is solubilized in the vehicle, with the suspended fraction representing about 5 weight % to about 80 weight % of the active agent and the second fraction representing about 20 weight % to about 95 weight % of the active agent. One or more additional active agents, which may be fully solubilized, partially solubilized, or suspended, may also be present. The first and second fractions of the active agent may or may not have different release profiles. Generally, a significant fraction of the solubilized drug will release rapidly, providing for rapid onset, while the suspended drug may be formulated for delayed and/or sustained release.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD [0083] gastrointestinal agents, such as alosetron, bisacodyl, cilansetron, cimetidine, cisapride, diphenoxylate, domperidone, **esomeprazole**, famotidine, granisetron, lansoprazole, loperamide, mesalazine, nizatidine, omeprazole, ondansetron, prantoprazole, rabeprazole sodium, ranitidine, risperidone, sulphasalazine, and tegaserod;

DETD [0220] The suspended fraction of the active agents is in the form of a plurality of solid particles, which may associate to form one or more larger dosage units such as a granule, pellet, bead or tablet, suspended in the vehicle. The particles may be single phase, or comprised of two or more phases. When the solid particles are wholly comprised of the

active agent, the particulate phase can be **amorphous** or in a high energy state, i.e., a metastable crystalline phase or a stable crystalline phase (wherein the crystalline state may include any of various polymorphs or solvates), or it may be a mixture of at least one **amorphous** phase and at least one crystalline phase. When the particles include one or more excipients, additives, or the like, the particulate material can be **amorphous**, crystalline, in the form of a solid solution with the excipient(s) and/or additive(s), or a mixture of two or more of these phases. The solid particles may contain a core comprised of the active agent, an excipient, or mixtures thereof, and may optionally be further coated with at least one layer of the active agent, the excipient, or mixtures thereof. The solid particles may be core-free, in the form of a powder or a plurality of granules, pellets, and/or beads, or combinations thereof.

DETD [0221] Any high energy phase in the particulate fraction may contain a phase stabilizing agent. Suitable phase stabilizing agents are typically: (1) hydrophilic polymers selected from the group consisting of (a) polyalkylene oxides, e.g., polyethylene glycol or ethylene glycol-propylene glycol copolymers), (b) polyalkylene oxide-substituted C.sub.2-C.sub.6 diols and triols, e.g., mono-poly(oxyethylene)-substituted propylene glycol, di-(polyoxyethylene)-substituted propylene glycol, mono-poly(oxyethylene)-substituted glycerol, di-(polyoxyethylene)-substituted glycerol, and tri-(polyoxyethylene)-substituted glycerol, (c) polyalkylene oxide-substituted saccharides such as polyoxyethylated sorbitol, and polyoxyethylated glucose, (d) poly(N-vinyl lactams) such as polyvinyl pyrrolidone and poly(N-vinyl caprolactam), (e) acidic polymers and salts and esters thereof, such as vinyl polymers having pending carboxylic acid, sulfonic acid or phosphonic acid groups, optionally esterified, ionized by association with a base, or otherwise derivatized (e.g., polystyrene sulfonate) and (f) polymers of carboxyvinyl monomers such as acrylic acid, methacrylic acid, and/or esters thereof; (2) surfactants such as any of those described in Section IIIA above; (3) saccharides, including monosaccharides, disaccharides and polysaccharides and derivatives thereof (e.g., dextran sulfate), with cellulosic polymers (e.g., hydroxypropylmethylcellulose) preferred; (4) gelatins; and (5) inorganic salts such as sodium chloride. Particulate material in an **amorphous** state may also include any of the above phase stabilizing agents in groups (1) through (5).

DETD [0224] That is, particulates comprised of solid solutions, **amorphous** mixtures, fused mixtures, eutectic compositions, or mixtures thereof can be prepared with similar polymers, lipids, sugars, and any other pharmaceutically acceptable excipients. In addition, solid particles comprising a water-soluble complex of an active agent with a complexing agent, such as cyclodextrin or a derivative thereof, can also be utilized in the present invention. In general, the solid solution, **amorphous** mixture, fused mixture, or eutectic composition should dissolve faster than the crystalline active agent alone. To further modify the release profile of the active agent from the active agent particles, size reduction and surface coatings can be applied. For example, a eutectic mixture formed from an active agent and an excipient using a melting and cooling process can be ground into smaller particles. These particles can then be spray-coated with a polymer to modify their surface and consequently the dissolution profile of the active agent. Additional details regarding suitable particle preparation techniques are described in the following section.

DETD [0290] The bile salt or acid in the present compositions and dosage forms may be an integral part of the formulation (e.g., included in the vehicle), or it may represent a coating on a dosage form, e.g., on a capsule, tablet, or caplet, or on each of a plurality of granules, beads, or pellets. The bile salt or acid may take any number of physical forms, e.g., it may be in crystalline, **amorphous**, nanosized,

micronized or milled form.

CLM What is claimed is:

29. The pharmaceutical formulation of claim 1, wherein the solid particles comprise at least one **amorphous** phase, at least one crystalline phase, or a mixture of at least one **amorphous** phase and at least one crystalline phase.

99. The pharmaceutical system of claim 74, wherein the solid particles comprise at least one **amorphous** phase, at least one crystalline phase, or a mixture of at least one **amorphous** phase and at least one crystalline phase.

L2 ANSWER 28 OF 42 USPATFULL on STN

ACCESSION NUMBER:	2003:26364 USPATFULL			
TITLE:	Potassium salt of (s)-**omeprazole**			
INVENTOR(S):	Nilsson, Maths, Sodertalje, SWEDEN			
PATENT ASSIGNEE(S):	AstraZeneca AB, Sodertalje, SWEDEN (non-U.S. corporation)			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6511996	B1	20030128	
	WO 2000044744		20000803	
APPLICATION INFO.:	US 2000-530248		20000426	(9)
	WO 2000-SE87		20000118	
	NUMBER		DATE	
PRIORITY INFORMATION:	SE 1999-274		19990128	
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	GRANTED			
PRIMARY EXAMINER:	Fan, Jane			
LEGAL REPRESENTATIVE:	White & Case LLP			
NUMBER OF CLAIMS:	9			
EXEMPLARY CLAIM:	1			
NUMBER OF DRAWINGS:	2 Drawing Figure(s); 2 Drawing Page(s)			
LINE COUNT:	304			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to a novel form of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole, known under the generic name omeprazole. More specifically, it relates to a novel crystalline form of the potassium salt of the (S)-enantiomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole. The present invention also relates to processes for preparing such a form of the potassium salt of (**S**)-**omeprazole** and pharmaceutical compositions containing it.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Potassium salt of (**s**)-**omeprazole**

AB The present invention relates to a novel form of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole, known under the generic name omeprazole. More specifically, it relates to a novel crystalline form of the potassium salt of the (S)-enantiomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole. The present invention also relates to processes for preparing such a form of the potassium salt of (**S**)-**omeprazole** and pharmaceutical compositions containing it.

SUMM The present invention relates to a novel form of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole, known under the generic name omeprazole. More specifically, it relates to a novel crystalline form of the potassium salt of the (S)-enantiomer

of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole. The present invention also relates to a process for preparing such a form of potassium salt of (S)-**omeprazole** and pharmaceutical compositions containing it.

SUMM Omeprazole is a sulfoxide and a chiral compound, wherein the sulfur atom is the stereogenic center. Thus, omeprazole is a racemic mixture of its two single enantiomers, the (R)- and (S)-enantiomer of omeprazole, herein referred to as (R)-omeprazole and (S)-**omeprazole**. The absolute configurations of the enantiomers of omeprazole have been determined by an X-ray study of an N-alkylated derivative of the (+)-enantiomer in non-salt form. The (+)-enantiomer of the non-salt form and the (-)-enantiomer of the non-salt form were found to have R and S configuration, respectively. The conditions for the optical rotation measurement for each of these enantiomers are described in WO 94/27988.

SUMM WO 96/02535 discloses a process for the preparation of the single enantiomers of omeprazole and structually related compounds as well as salts thereof WO 96/01623 discloses pharmaceutical dosage forms comprising for instance magnesium salts of (R)-and (S)-**omeprazole**.

SUMM WO 98/54171 discloses a process for the preparation of the trihydrate of magnesium salt of (S)-**omeprazole**, wherein the potassium salt of (S)-**omeprazole** is used as an intermediate. The potassium salt of (S)-**omeprazole**, according to the prior art, crystallizes as a methanol solvate.

SUMM Certain salts of of (S)-**omeprazole**, such as the potassium salt, are in general suitable compounds for i.v.-administration due to their intrinsic properties, such as high stability and high solubility in water. Methanol solvates are however not suitable for i.v.-administration, since the concomitant administration of methanol could be fatal for the receiver. Therefore there exists a need for a potassium salt of (S)-omeprazol that is free from methanol.

SUMM The novel form of the potassium salt of (S)-**omeprazole** according to the present invention is hereinafter referred to as the potassium salt of (S)-**omeprazole** form B. The prior art form of the potassium salt of (S)-**omeprazole** disclosed in WO 98/54171 is hereinafter referred to as the potassium salt of (S)-**omeprazole** form A.

DRWD FIG. 1 is an X-ray powder diffractogram of the potassium salt of (S)-**omeprazole** prepared according to the present invention, i.e. form B.

DRWD FIG. 2 is an X-ray powder diffractogram of the potassium salt of (S)-**omeprazole** prepared according to example 2 in WO 98/54171, i.e. form A.

DETD It has surprisingly been found that the potassium salt of (S)-**omeprazole** occurs in a number of structurally different forms. It is an object of the present invention to provide a substantially pure potassium salt of (S)-**omeprazole** form B.

DETD The potassium salt of (S)-**omeprazole** form B is advantageous because it is hydrate form, is while the previous known form A is methanol solvate. The potassium salt of (S)-**omeprazole** form B is especially suitable for intravenous administration. The potassium salt of (S)-**omeprazole** form B is further characterized by being crystalline, and preferably being highly crystalline.

DETD The potassium salt of (S)-**omeprazole** form B, obtained according to the present invention, is substantially free from other forms of potassium salts of (S)-**omeprazole**, such as the corresponding form A described in the prior art The potassium salt of (S)-**omeprazole** form B obtained according to the present invention is also substantially free from potassium salts of (R)-omeprazole.

DETD The potassium salt of (S)-**omeprazole** form B is characterized by the positions and intensities of the major peaks in the X-ray powder diffractogram, but may also be characterized by conventional FT-IR spectroscopy. These characteristics are not exhibited by any other forms of potassium salt of (S)-**omeprazole** and accordingly, the potassium salt of (S)-**omeprazole** form B is easily distinguishable from any other crystal forms of potassium salts of (S)-**omeprazole** disclosed in prior art. With the expression "any form" is meant anhydrates, hydrates, solvates, **amorphous** forms, and polymorphs. Such examples of any forms of potassium salt of (S)-**omeprazole** includes, but are not limited to, anhydrates, monohydrates, dihydrates, sesquihydrates, trihydrates, alcoholates, such as methanolates and ethanolates, **amorphous** forms and polymorphs.

DETD The potassium salt of (S)-**omeprazole** form B may also be characterized by its unit cell.

DETD In a further aspect, the present invention provides a process for the preparation of the potassium salt of (S)-**omeprazole** form B which comprises the step of converting (S)-**omeprazole** into the corresponding potassium salt in toluene or dichloromethane by treatment with a potassium source, such as potassium hydroxide or potassium methylate, followed by isolation of the formed salt.

DETD The crude (S)-**omeprazole** used in the process can for example be prepared by oxidizing 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole into (S)-**omeprazole**, with an oxidizing agent and a chiral titanium complex, optionally in the presence of a base in an organic solvent, such as toluene or dichloromethane, as is described in the prior art, see WO 98/54171.

DETD The potassium salt of (S)-**omeprazole** form B, prepared according to the present invention is analyzed, characterized and differentiated from the previous known form A by X-ray powder diffraction, a technique which is known per se. Another suitable technique to analyze, characterize and differentiate the potassium salt of (S)-**omeprazole** form B from the corresponding form A is by conventional FT-IR.

DETD The amount of water in the potassium salt of (S)-**omeprazole** form B is determined by thermogravimetric analysis (TGA), a technique which is known per se.

DETD The potassium salt of (S)-**omeprazole** form B is effective as a gastric acid secretion inhibitor, and is useful as an antiulcer agent. In a more general sense, it can be used for treatment of gastric-acid related conditions in mammals and especially in man, including e.g. reflux esophagitis, gastritis, duodenitis, gastric ulcer and duodenal ulcer. Furthermore, it may be used for treatment of other gastrointestinal disorders where gastric acid inhibitory effect is desirable e.g. in patients on non-steroidal anti-inflammatory drug (NSAID) therapy, in patients with Non Ulcer Dyspepsia, in patients with symptomatic gastro-esophageal reflux disease, and in patients with gastrinomas. The potassium salt of (S)-**omeprazole** form B may also be used in patients in intensive care situations, in patients with acute upper gastrointestinal bleeding, pre- and postoperatively to prevent aspiration of gastric acid and to treat stress ulceration. Further, the potassium salt of (S)-

omeprazole form B may be useful in the treatment of psoriasis as well as in the treatment of Helicobacter infections and diseases related to these. The potassium salt of (S)-**omeprazole** form B may also be used for treatment of inflammatory conditions in mammals, including man.

DETD Any suitable route of administration may be employed for providing the patient with an effective dosage of the potassium salt of (S)-**omeprazole** form B, according to the present invention. For example, peroral or parenteral formulations and the like may be employed. Dosage forms include capsules, tablets, dispersions, suspensions and the like. The potassium salt of (S)-**omeprazole** form B is, because of being highly soluble in water, especially suitable for parenteral formulations, such as i.v.

DETD According to the invention there is further provided a pharmaceutical composition comprising the potassium salt of (S)-**omeprazole** form B, as active ingredient, in association with a pharmaceutically acceptable carrier, diluent or excipient and optionally other therapeutic ingredients. Compositions comprising other therapeutic ingredients are especially of interest in the treatment of Helicobacter infections. The invention also provides the use of the potassium salt of (S)-**omeprazole** form B in the manufacture of a medicament for use in the treatment of a gastric-acid related condition and a method of treating a gastric-acid related condition which method comprises administering to a subject suffering from said condition a therapeutically effective amount of the potassium salt of (S)-**omeprazole** form B.

DETD In the practice of the invention, the most suitable route of administration as well as the magnitude of a therapeutic dose of the potassium salt of (S)-**omeprazole** form B in any given case will depend on the nature and severity of the disease to be treated. The dose, and dose frequency, may also vary according to the age, body weight, and response of the individual patient. Special requirements may be needed for patients having Zollinger-Ellison syndrome, such as a need for higher doses than the average patient. Children and patients with liver diseases as well as patients under long term treatment will generally benefit from doses that are somewhat lower than the average. Thus, in some conditions it may be necessary to use doses outside the ranges stated below. Such higher and lower doses are within the scope of the present invention.

DETD Combination therapies comprising the potassium salt of (S)-**omeprazole** form B and other active ingredients in separate dosage forms may also be used. Examples of such active ingredients include anti-bacterial compounds, non-steroidal anti-inflammatory agents, antacid agents, alginates and prokinetic agents.

DETD The examples which follow will further illustrate the preparation of the compound of the invention, i.e. the potassium salt of (S)-**omeprazole** form B, but are not intended to limit the scope of the invention as defined hereinabove or as claimed below.

DETD Potassium Salt of (S)-**omeprazole** Form B

DETD Approximately 2 % (w/w) of the water content is incorporated in the crystal lattice (i.e. .about.0,5 H.sub.2O/ molecule of potassium salt of (S)-**omeprazole** form B)

DETD The peaks, identified with d-values calculated from the Bragg formula and intensities, have been extracted from the diffractogram of the potassium salt of (S)-**omeprazole** form B. The relative intensities are less reliable and instead of numerical values the following definitions are used;

CLM What is claimed is:

1. The potassium salt of (S)-**omeprazole** form B, wherein the compound is in a hydrate form and provides an X-ray powder diffraction pattern exhibiting substantially the following d-values:

d-value [Å] Intensity

9.6 very strong
8.0 Strong
7.9 Strong
7.5 Weak
7.3 Weak
7.2 very strong
5.9 Strong
5.6 Strong
5.2 Strong
5.1 very strong
4.88 Weak
4.83 Weak
4.71 Weak
4.67 Weak
4.55 medium
4.49 Strong
4.39 Strong
4.15 Weak
4.10 Weak
3.95 Weak
3.74 very strong
3.67 Medium
3.58 Strong
3.55 Medium
3.47 Strong
3.40 Weak
3.27 Strong
3.20 Medium
3.15 Medium
3.10 Weak
3.03 Weak
2.98 Medium
2.87 Medium
2.85 Medium
2.38 Medium
2.30 Weak.

2. The potassium salt of (S)-**omeprazole** form B according to claim 1, wherein the compound is in a crystalline form.

3. A process for the preparation of potassium salt of (S)-**omeprazole** form B as claimed in claim 1 or 2, which comprises the step of converting (S)-**omeprazole** into the corresponding potassium salt in toluene or dichloromethane by treatment with a potassium source, followed by isolation of the formed salt, wherein a substantially methanol-free system is used.

4. A process according to claim 3, wherein (S)-**omeprazole** is obtained by oxidizing 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole, with an oxidizing agent and a chiral titanium complex, optionally in the presence of a base in an organic solvent.

5. A pharmaceutical formulation comprising the potassium salt of (S)-**omeprazole** form B as claimed in claim 1 or 2 in admixture with a pharmaceutically acceptable excipient.

6. A pharmaceutical formulation comprising a therapeutically effective a mount of the potassium salt of (S)-**omeprazole** form B

as claimed in claim 1 or 2 in admixture with a pharmaceutically acceptable excipient.

7. A method for inhibiting gastric acid secretion which comprises administration of a therapeutically effective amount of the potassium salt of (S)-**omeprazole** form B as claimed in claim 1 or 2 to a patient in need of such inhibition.

8. A method for the treatment of gastrointestinal inflammatory diseases which comprises administering a therapeutically effective amount of the potassium salt of (S)-**omeprazole** form B as claimed in claim 1 or 2 to a patient in need of such treatment.

9. A method for the treatment of conditions involving infection by Helicobacter pylori of human gastric mucosa, which comprises administering a therapeutically effective amount of the potassium salt of (S)-**omeprazole** as claimed in claim 1 or 2 to a patient in need of such treatment.

L2 ANSWER 29 OF 42 USPATFULL on STN
ACCESSION NUMBER: 2003:4149 USPATFULL
TITLE: Process
INVENTOR(S): Kronstrom, Anders, Stockholm, SWEDEN
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	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003004190	A1	20030102
	US 6747155	B2	20040608
APPLICATION INFO.:	US 2002-113245	A1	20020401 (10)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1998-77719, filed on 8 Jun 1998, GRANTED, Pat. No. US 6369085 A 371 of International Ser. No. WO 1998-SE974, filed on 5 May 1998, UNKNOWN

	NUMBER	DATE
PRIORITY INFORMATION:	SE 1997-2065	19970530

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: WHITE & CASE LLP, PATENT DEPARTMENT, 1155 AVENUE OF THE AMERICAS, NEW YORK, NY, 10036
NUMBER OF CLAIMS: 7
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 5 Drawing Page(s)
LINE COUNT: 554
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to a novel process for the preparation of the magnesium salt of the (-)-enantiomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole trihydrate, ie. **S-omeprazole** magnesium salt trihydrate. The present invention also relates to the **S-omeprazole** magnesium salt trihydrate prepared in accordance with the new process and pharmaceutical compositions containing it. Furthermore, the present invention also relates to new intermediates used in the process.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to a novel process for the preparation of

the magnesium salt of the (-)-enantiomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole trihydrate, ie. **S-omeprazole** magnesium salt trihydrate. The present invention also relates to the **S-omeprazole** magnesium salt trihydrate prepared in accordance with the new process and pharmaceutical compositions containing it. Furthermore, the present invention also relates to new intermediates used in the process.

SUMM [0002] The present invention relates to a novel process for preparing the magnesium salt of the (-)-enantiomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfmyl]-1H-benzimidazole trihydrate, i.e. **S-omeprazole** magnesium salt trihydrate. The present invention also relates to the **S-omeprazole** magnesium salt trihydrate prepared in accordance with the novel process and pharmaceutical compositions containing it. Furthermore, the present invention also relates to intermediates used in the process, and their preparation.

SUMM [0004] Omeprazole is a sulfoxide and a chiral compound, wherein the sulfur atom being the stereogenic center. Thus, omeprazole is a racemic mixture of its two single enantiomers, the R and S-enantiomer of omeprazole, herein referred to as R-omeprazole and **S-omeprazole**. The absolute configurations of the enantiomers of omeprazole have been determined by an X-ray study of an N-alkylated derivative of the (+)-enantiomer in non-salt form. The (+)-enantiomer of the non-salt form and the (-)-enantiomer of the non-salt form were found to have R and S configuration, respectively, and the (+)-enantiomer of the magnesium salt and the (-)-enantiomer of the magnesium salt were also found to have R and S configuration, respectively. The conditions for the optical rotation measurement for each of these enantiomers are described in WO 94/27988.

SUMM [0006] WO 96/02535 discloses a process for the preparation of the single enantiomers of omeprazole and salts thereof, and WO 96/01623 discloses a suitable tableted dosage forms of for instance magnesium salts of R- and **S-omeprazole**.

DRWD [0007] FIG. 1 shows a X-ray powder diffractogram of the magnesium salt of **S-omeprazole** trihydrate prepared according to the present invention.

DRWD [0008] FIG. 2 shows a X-ray powder diffractogram of the potassium salt of **S-omeprazole** prepared and used in the present application (See examples 2 and 3)

DRWD [0009] FIG. 3 shows a X-ray powder diffractogram of a magnesium salt of **S-omeprazole** dihydrate prepared and used in the present application (See example 5)

DRWD [0010] FIG. 4 shows a X-ray powder diffractogram of a magnesium salt of **S-omeprazole** dihydrate which is a polymorph of the dihydrate shown in FIG. 3 (See Example 6). This magnesium salt of **S-omeprazole** dihydrate has been prepared and can be used in the preparation of the magnesium salt of **S-omeprazole** trihydrate according to the present invention.

DRWD [0011] FIG. 5 shows X-ray powder diffractogram of the magnesium salt of **S-omeprazole** prepared according to example A in WO 96/01623.

DETD [0012] It has surprisingly been found that the magnesium salt of **S-omeprazole** occurs in a number of structurally different forms. It is an object of the present invention to provide a substantially pure magnesium salt of **S-omeprazole** trihydrate, hereinafter referred to as the compound of the invention. This trihydrate can be obtained as a well defined compound. The present invention also provides a process to obtain and a method of differentiating the magnesium salt of **S-omeprazole**

trihydrate from other forms of magnesium salts of **S-omeprazole**.

DETD [0014] The magnesium salt of **S-omeprazole** trihydrate obtained according to the present invention is substantially free from magnesium salts of R-omeprazole. The magnesium salt of **S-omeprazole** trihydrate obtained according to the present invention is also substantially free from other forms of magnesium salts of **S-omeprazole**, such as the corresponding magnesium salt compounds described in prior art, and dihydrates used in the preparation of the trihydrate compound according to the present invention.

DETD [0015] The compound of the invention is characterized by the positions and intensities of the major peaks in the X-ray powder diffractogram, but may also be characterized by conventional FT-IR spectroscopy. These characteristics are not exhibited by any other form of magnesium salt of **S-omeprazole** and accordingly, the magnesium salt of **S-omeprazole** trihydrate is easily distinguishable from any other crystal form of the magnesium salt of **S-omeprazole** disclosed in prior art. The compound of the invention is characterized by being highly crystalline, i.e. having a higher crystallinity than any other form of magnesium salt of **S-omeprazole** disclosed in the prior art. With the expression "any other form" is meant anhydrates, hydrates, solvates, and polymorphs or **amorphous** forms thereof disclosed in the prior art. Examples of any other forms of magnesium salt of **S-omeprazole** includes, but are not limited to, anhydrates, monohydrates, dihydrates, sesquihydrates, trihydrates, alcoholates, such as methanolates and ethanolates, and polymorphs or **amorphous** forms thereof.

DETD [0017] In a further aspect, the present invention provides processes for the preparation of the magnesium salt of **S-omeprazole** trihydrate which comprises;

DETD [0018] a) treating a magnesium salt of **S-omeprazole** of any form, for example prepared according to procedures known in the art such as Example A in WO 96/01623 which is incorporated herein by reference, with water at a suitable temperature for a suitable time. By a suitable temperature is meant a temperature, which induces the transformation of starting material to product without decomposing any of these compounds. Examples of such suitable temperatures include, but are not limited to, room temperature and above. By a suitable time is meant a time that results in high conversion of the starting material into product without causing any decomposition of either compounds, i.e. results in a good yield. This suitable time will vary depending on the temperature used in a way well known to people in the art. The higher the temperature, the shorter time is needed to give the desired conversion. The amount of water is not crucial and will depend on the process conditions used. The magnesium salt of **S-omeprazole** trihydrate is thereafter separated from the aqueous slurry, for example by filtration or centrifugation and thereafter dried to constant weight; or

DETD [0021] The resulting potassium salt of **S-omeprazole** is thereafter converted to the corresponding magnesium salt by treatment with a magnesium source, such as magnesium sulfate in a lower alcohol, such as methanol. The solution is optionally filtered and the precipitation is initialized by addition of a non-solvent such as acetone. The product is filtered off and optionally washed with water and further processed as is described in a) above. Alternatively, the potassium salt may be treated with a magnesium source, such as magnesium sulfate in water, and isolation of the magnesium salt of **S-omeprazole** trihydrate, or any other conventional technique for transforming a potassium salt to the corresponding magnesium salt can be used and is within the scope of the present invention.

DETD [0022] One process for obtaining **esomeprazole** magnesium

trihydrate is described in Example 7. In this example, the aqueous solution of magnesium sulfate is added to an aqueous solution of **esomeprazole** potassium. However, the resulting solution is a foamy mixture. This foaming tendency of the mixture makes the process exceptionally difficult to scale up. Surprisingly, it has now have found that a reversed order of addition, i.e., adding an aqueous solution of **esomeprazole** potassium to an aqueous solution of magnesium sulfate, provides a method where the foaming is advantageously and substantially reduced to minor proportions. Thus, by this reversed order of addition as exemplified by Example 8, it is possible to effortlessly scale up the process for large production.

DETD [0023] Yet a further aspect of the present invention is to provide a suitable intermediate used in the preparation of the compound of the invention, as well as a process for its preparation. The potassium salt of **S-omeprazole** is found to be such a suitable intermediate. The potassium salt of **S-omeprazole** may also be used as an active component of a pharmaceutical formulation to be used in the treatment of gastrointestinal diseases.

DETD [0024] The compound of the invention, i.e. the magnesium salt of **S-omeprazole** trihydrate, prepared according to the present invention may be analyzed by XRPD, a technique which is known per se.

DETD [0025] The amount of water in the magnesium salt of **S-omeprazole** trihydrate is determined by thermogravimetric analysis, a technique which is known per se.

DETD [0027] Any suitable route of administration may be employed for providing the patient with an effective dosage of the magnesium salt of **S-omeprazole** trihydrate, according to the invention. For example, peroral or parental formulations and the like may be employed. Dosage forms include capsules, tablets, dispersions, suspensions and the like.

DETD [0028] It is further provided a pharmaceutical composition comprising the magnesium salt of **S-omeprazole** trihydrate according to the invention, as active ingredient, in association with a pharmaceutically acceptable carrier, diluent or excipient and optionally other therapeutic ingredients. Compositions comprising other therapeutic ingredients are especially of interest in the treatment of Helicobacter infections. The invention also provides the use of the magnesium salt of **S-omeprazole** trihydrate of the invention in the manufacture of a medicament for use in the treatment of a gastric-acid related condition and a method of treating a gastric-acid related condition which method comprises administering to a subject suffering from said condition a therapeutically effective amount of the magnesium salt of **S-omeprazole** trihydrate according to the invention.

DETD [0030] In the practice of the invention, the most suitable route of administration as well as the magnitude of a therapeutic dose of the magnesium salt of **S-omeprazole** trihydrate according to the invention in any given case will depend on the nature and severity of the disease to be treated. The dose, and dose frequency, may also vary according to the age, body weight, and response of the individual patient. Special requirements may be needed for patients having Zollinger-Ellison syndrome, such as a need for higher doses than the average patient. Children and patients with liver diseases generally will benefit from doses that are somewhat lower than the average. Thus, in some conditions it may be necessary to use doses outside the ranges stated below, for example long term treatments may request lower dosage. Such higher and lower doses are within the scope of the present invention. Such daily doses may vary between 5 mg to 300 mg.

DETD [0033] Combination preparations comprising the magnesium salt of **S-omeprazole** trihydrate and other active ingredients may also be used. Examples of such active ingredients include, but are

not limited to anti-bacterial compounds, non-steroidal anti-inflammatory agents, antacid agents, alginates and prokinetic agents.

DETD [0036] Water (157 kg) was added to the wet crystals of the magnesium salt of **S-omeprazole**, prepared 0 according to Example 4, below. The mixture was heated to 38° C. with stirring and left for 3 hours. The crystals were filtered off and dried in vacuo. Yield: 31.6 kg

DETD [0038] Some additional very weak peaks found in the diffractogram have been omitted from table 1.

TABLE 1

Positions and intensities of the major peaks in the XRP-diffractogram of the magnesium salt of **S-omeprazole** trihydrate.

d-value/Å	Relative Intensity
2.67	M
2.79	M
3.27	M
3.52	S
3.82	S
3.96	Vs
4.14	M
5.2	M
5.6	M
6.7	Vs
6.9	S
8.3	W
16.6	Vs

DETD [0045] The products from Examples 2 and 3 were analysed using X-ray powder diffraction as described in Example 1 and gave the diffractogram depicted in FIG. 2 and given below in Table 2. Some additional very weak peaks found in the diffractogram have been omitted from Table 2.

TABLE 2

Positions and intensities of the major peaks in the XRP-diffractogram of the potassium salt of **S-omeprazole.**

d-value/Å	Relative intensity	d-value/ (Å)	Relative intensity	
13.6	Vs	3.52	m	
10.6	Vw	3.42	w	
7.8	M	3.38	w	
6.8	M	3.34	m	
6.5	M	3.28	w	
6.2	W	3.20	m	
6.1	M	3.12	w	
5.8	S	3.06	w	
5.4	M	3.03	w	
5.3	W	2.97	w	$\alpha 1$ = 1.54060 Å
5.2	W	2.93	vw	
5.0	Vw	2.89	w	
4.75	M	2.85	m	
4.71	W	2.76	w	
4.52	W	2.71	vw	
4.42	W	2.66	vw	
4.32	W	2.58	w	
4.27	M	2.57	w	
3.98	Vw	2.56	w	
3.92	W	2.52	vw	
3.89	W	2.47	vw	

3.87	W	2.45	vw
3.81	W	2.43	vw
3.74	M	2.40	vw
3.60	M	2.38	vw
3.55	M	2.31	vw

DETD [0050] The product was analyzed using X-ray powder diffraction as described in Example 1, and the analyze gave the diffractogram depicted in FIG. 3 and given below in Table 3. Some additional peaks with low intensities found in the diffractogram have been omitted from Table 3.

TABLE 3

Positions and intensities of the major peaks in the XRP-diffractogram of the magnesium salt of **S-omeprazole** dihydrate, Form B.

d-value/Å	Relative Intensity
4.19	M
4.45	M
4.68	M
4.79	S
4.91	S
4.98	S
5.1	M
5.4	S
5.5	M
5.6	M
5.8	M
6.3	M
6.7	S
7.9	M
8.1	S
11.0	M
11.8	M
14.9	Vs

DETD [0051] Convertion of Magnesium Salt of **S-Omeprazole** Dihydrate to Trihydrate

DETD [0055] The product was analyzed using X-ray powder diffration as described in Example 1 and gave the diffractogram depicted in FIG. 4 and given below in Table 4. Some additional peaks with low intensities found in the diffractogram have been omitted from Table 4.

TABLE 4

Positions and intensities of the major peaks in the XRP-diffractogram of the magnesium salt of **S-omeprazole** dihydrate, Form A.

d-value/Å	Relative Intensity
3.04	S
3.14	S
3.18	M
4.05	S
4.19	S
4.32	M
4.54	S
4.69	Vs
5.2	S
5.3	S
5.8	S
6.2	Vs
6.6	S
15.5	Vs

CLM What is claimed is:

1. A process for the preparation of the magnesium salt of **S-omeprazole** trihydrate which comprises the following steps: (a) dissolving a magnesium source in water; (b) mixing a potassium salt of **S-omeprazole** with water; (c) adding the solution of the potassium salt of **S-omeprazole** of step (b) to the solution of step (a) to convert the potassium salt of **S-omeprazole** into the corresponding magnesium salt of **S-omeprazole** and precipitate the magnesium salt of **S-omeprazole**; (d) isolating the obtained magnesium salt of **S-omeprazole**; (e) treating the obtained magnesium salt of **S-omeprazole** with water; and (f) isolating and drying the obtained magnesium salt of **S-omeprazole** trihydrate.

2. The process according to claim 1, further comprising the step of adding seeding crystals of **S-omeprazole** magnesium salt trihydrate to the solution of step (a).

7. The process according to any one of claims 1-4, wherein the magnesium salt of **S-omeprazole** trihydrate is characterized by the following major peaks in its X-ray diffractogram:

d-value/Å	Relative Intensity
2.67	m
2.79	m
3.27	m
3.52	s
3.82	s
3.96	vs
4.14	m
5.2	m
5.6	m
6.7	vs
6.9	s
8.3	w
16.6	vs

L2 ANSWER 30 OF 42 USPATFULL on STN
ACCESSION NUMBER: 2002:344508 USPATFULL
TITLE: Potassium salt of **S-omeprazole**
INVENTOR(S): Kronstrom, Anders, Stockholm, SWEDEN
Leander, Eva, Skiptvet, NORWAY
Mattson, Anders, Taby, SWEDEN

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002198239	A1	20021226
	US 6677455	B2	20040113
APPLICATION INFO.:	US 2002-76711	A1	20020214 (10)

RELATED APPLN. INFO.: Division of Ser. No. US 1998-77719, filed on 8 Jun 1998, GRANTED, Pat. No. US 6369085 A 371 of International Ser. No. WO 1998-SE974, filed on 5 May 1998, UNKNOWN

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PRIORITY INFORMATION:	SE 1997-2065	19970530

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: WHITE & CASE LLP, PATENT DEPARTMENT, 1155 AVENUE OF THE AMERICAS, NEW YORK, NY, 10036
NUMBER OF CLAIMS: 11
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 5 Drawing Page(s)
LINE COUNT: 589
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to a novel form of the (-)-enantiomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole, i.e. **S-omeprazole**. More specifically, it relates to a novel form of the magnesium salt of the S-enantiomer of omeprazole trihydrate. The present invention also relates to processes for preparing such a form of the magnesium salt of **S-omeprazole** and pharmaceutical compositions containing it. Furthermore, the present invention also relates to new intermediates used in the process.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Potassium salt of **S-omeprazole**

AB The present invention relates to a novel form of the (-)-enantiomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole, i.e. **S-omeprazole**. More specifically, it relates to a novel form of the magnesium salt of the S-enantiomer of omeprazole trihydrate. The present invention also relates to processes for preparing such a form of the magnesium salt of **S-omeprazole** and pharmaceutical compositions containing it. Furthermore, the present invention also relates to new intermediates used in the process.

SUMM [0002] The present invention relates to a novel form of the (-)-enantiomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole, i.e. **S-omeprazole**. More specifically, it relates to a novel form of the magnesium salt of the S-enantiomer of omeprazole trihydrate. The present invention also relates to processes for preparing such a form of the magnesium salt of **S-omeprazole** and pharmaceutical compositions containing it. Furthermore, the present invention also relates to intermediates used in the process, and their preparation.

SUMM [0004] Omeprazole is a sulfoxide and a chiral compound, wherein the sulfur atom being the stereogenic center. Thus, omeprazole is a racemic mixture of its two single enantiomers, the R and S-enantiomer of omeprazole, herein referred to as R-omeprazole and **S-omeprazole**. The absolute configurations of the enantiomers of omeprazole have been determined by an X-ray study of an N-alkylated derivative of the (+)-enantiomer in non-salt form. The (+)-enantiomer of the non-salt form and the (-)-enantiomer of the non-salt form were found to have R and S configuration, respectively, and the (+)-enantiomer of the magnesium salt and the (-)-enantiomer of the magnesium salt were also found to have R and S configuration, respectively. The conditions for the optical rotation measurement for each of these enantiomers are described in WO 94/27988.

SUMM [0006] WO 96/02535 discloses a process for the preparation of the single enantiomers of omeprazole and salts thereof, and WO 96/01623 discloses a suitable tableted dosage forms of for instance magnesium salts of R- and **S-omeprazole**.

DRWD [0007] FIG. 1 shows a X-ray powder diffractogram of the magnesium salt of **S-omeprazole** trihydrate prepared according to the present invention.

DRWD [0008] FIG. 2 shows a X-ray powder diffractogram of the potassium salt

of **S-omeprazole** prepared and used in the present application (See examples 2 and 3)

DRWD [0009] FIG. 3 shows a X-ray powder diffractogram of a magnesium salt of **S-omeprazole** dihydrate prepared and used in the present application (See example 5)

DRWD [0010] FIG. 4 shows a X-ray powder diffractogram of a magnesium salt of **S-omeprazole** dihydrate which is a polymorph of the dihydrate shown in FIG. 3 (See Example 6). This magnesium salt of **S-omeprazole** dihydrate has been prepared and can be used in the preparation of the magnesium salt of **S-omeprazole** trihydrate according to the present invention.

DRWD [0011] FIG. 5 shows X-ray powder diffractogram of the magnesium salt of **S-omeprazole** prepared according to example A in WO 96/01623.

DETD [0012] It has surprisingly been found that the magnesium salt of **S-omeprazole** occurs in a number of structurally different forms. It is an object of the present invention to provide a substantially pure magnesium salt of **S-omeprazole** trihydrate, hereinafter referred to as the compound of the invention. This trihydrate can be obtained as a well defined compound. The present invention also provides a process to obtain and a method of differentiating the magnesium salt of **S-omeprazole** trihydrate from other forms of magnesium salts of **S-omeprazole.**

DETD [0014] The magnesium salt of **S-omeprazole** trihydrate obtained according to the present invention is substantially free from magnesium salts of R-omeprazole. The magnesium salt of **S-omeprazole** trihydrate obtained according to the present invention is also substantially free from other forms of magnesium salts of **S-omeprazole**, such as the corresponding magnesium salt compounds described in prior art, and dihydrates used in the preparation of the trihydrate compound according to the present invention.

DETD [0015] The compound of the invention is characterized by the positions and intensities of the major peaks in the X-ray powder diffractogram, but may also be characterized by conventional FT-IR spectroscopy. These characteristics are not exhibited by any other form of magnesium salt of **S-omeprazole** and accordingly, the magnesium salt of **S-omeprazole** trihydrate is easily distinguishable from any other crystal form of the magnesium salt of **S-omeprazole** disclosed in prior art. The compound of the invention is characterized by being highly crystalline, i.e. having a higher crystallinity than any other form of magnesium salt of **S-omeprazole** disclosed in the prior art. With the expression "any other form" is meant anhydrates, hydrates, solvates, and polymorphs or **amorphous** forms thereof disclosed in the prior art. Examples of any other forms of magnesium salt of **S-omeprazole** includes, but are not limited to, anhydrates, monohydrates, dihydrates, sesquihydrates, trihydrates, alcoholates, such as methanolates and ethanolates, and polymorphs or **amorphous** forms thereof.

DETD [0017] In a further aspect, the present invention provides processes for the preparation of the magnesium salt of **S-omeprazole** trihydrate which comprises:

DETD [0018] a) treating a magnesium salt of **S-omeprazole** of any form, for example prepared according to procedures known in the art such as Example A in WO 96/01623 which is incorporated herein by reference, with water at a suitable temperature for a suitable time. By a suitable temperature is meant a temperature which induces the transformation of starting material to product without decomposing any of these compounds. Examples of such suitable temperatures include, but are not limited to, room temperature and above. By a suitable time is meant a time that results in high conversion of the starting material

into product without causing any decomposition of either compounds, i.e. results in a good yield. This suitable time will vary depending on the temperature used in a way well known to people in the art. The higher the temperature, the shorter time is needed to give the desired conversion. The amount of water is not crucial and will depend on the process conditions used. The magnesium salt of **S-omeprazole** trihydrate is thereafter separated from the aqueous slurry, for example by filtration or centrifugation and thereafter dried to constant weight; or

DETD [0021] The resulting potassium salt of **S-omeprazole** is thereafter converted to the corresponding magnesium salt by treatment with a magnesium source, such as magnesium sulfate in a lower alcohol, such as methanol. The solution is optionally filtered and the precipitation is initialized by addition of a non-solvent such as acetone. The product is filtered off and optionally washed with water and further processed as is described in a) above. Alternatively, the potassium salt may be treated with a magnesium source, such as magnesium sulfate in water, and isolation of the magnesium salt of **S-omeprazole** trihydrate, or any other conventional technique for transforming a potassium salt to the corresponding magnesium salt can be used and is within the scope of the present invention.

DETD [0022] Yet a further aspect of the present invention is to provide a suitable intermediate used in the preparation of the compound of the invention, as well as a process for its preparation. The potassium salt of **S-omeprazole** is found to be such a suitable intermediate. The potassium salt of **S-omeprazole** may also be used as an active component of a pharmaceutical formulation to be used in the treatment of gastrointestinal diseases.

DETD [0023] The compound of the invention, i.e. the magnesium salt of **S-omeprazole** trihydrate, prepared according to the present invention may be analyzed by XRPD, a technique which is known per se.

DETD [0024] The amount of water in the magnesium salt of **S-omeprazole** trihydrate is determined by thermogravimetric analysis, a technique which is known per se.

DETD [0026] Any suitable route of administration may be employed for providing the patient with an effective dosage of the magnesium salt of **S-omeprazole** trihydrate, according to the invention. For example, peroral or parental formulations and the like may be employed. Dosage forms include capsules, tablets, dispersions, suspensions and the like.

DETD [0027] It is further provided a pharmaceutical composition comprising the magnesium salt of **S-omeprazole** trihydrate according to the invention, as active ingredient, in association with a pharmaceutically acceptable carrier, diluent or excipient and optionally other therapeutic ingredients. Compositions comprising other therapeutic ingredients are especially of interest in the treatment of Helicobacter infections. The invention also provides the use of the magnesium salt of **S-omeprazole** trihydrate of the invention in the manufacture of a medicament for use in the treatment of a gastric-acid related condition and a method of treating a gastric-acid related condition which method comprises administering to a subject suffering from said condition a therapeutically effective amount of the magnesium salt of **S-omeprazole** trihydrate according to the invention.

DETD [0029] In the practice of the invention, the most suitable route of administration as well as the magnitude of a therapeutic dose of the magnesium salt of **S-omeprazole** trihydrate according to the invention in any given case will depend on the nature and severity of the disease to be treated. The dose, and dose frequency, may also vary according to the age, body weight, and response of the individual patient. Special requirements may be needed for patients

having Zollinger-Ellison syndrome, such as a need for higher doses than the average patient. Children and patients with liver diseases generally will benefit from doses that are somewhat lower than the average. Thus, in some conditions it may be necessary to use doses outside the ranges stated below, for example long term treatments may request lower dosage. Such higher and lower doses are within the scope of the present invention. Such daily doses may vary between 5 mg to 300 mg.

DETD [0032] Combination preparations comprising the magnesium salt of **S-omeprazole** trihydrate and other active ingredients may also be used. Examples of such active ingredients include, but are not limited to anti-bacterial compounds, non-steroidal anti-inflammatory agents, antacid agents, alginates and prokinetic agents.

DETD [0035] Water (157 kg) was added to the wet crystals of the magnesium salt of **S-omeprazole**, prepared according to Example 4, below. The mixture was heated to 38° C. with stirring and left for 3 hours. The crystals were filtered off and dried in vacuo. Yield: 31.6 kg

DETD [0037] Some additional very weak peaks found in the diffractogram have been omitted from table 1.

TABLE 1

Positions and intensities of the major peaks in the XRP-diffractogram of the magnesium salt of **S-omeprazole** trihydrate.

d-value/Å	Relative Intensity
2.67	m
2.79	m
3.27	m
3.52	s
3.82	s
3.96	vs
4.14	m
5.2	m
5.6	m
6.7	vs
6.9	s
8.3	w
16.6	vs

DETD [0044] The products from Examples 2 and 3 were analyzed using X-ray powder diffraction as described in Example 1 and gave the diffractogram depicted in FIG. 2 and given below in Table 2. Some additional very weak peaks found in the diffractogram have been omitted from Table 2.

TABLE 2

Positions and intensities of the major peaks in the XRP-diffractogram of the potassium salt of **S-omeprazole.**

d-value/Å	Relative intensity	d-value/ (Å)	Relative intensity
13.6	vs	3.52	m
10.6	vw	3.42	w
7.8	m	3.38	w
6.8	m	3.34	m
6.5	m	3.28	w
6.2	w	3.20	m
6.1	m	3.12	w
5.8	s	3.06	w
5.4	m	3.03	w
5.3	w	2.97	w
5.2	w	2.93	vw

5.0	vw	2.89	w
4.75	m	2.85	m
4.71	w	2.76	w
4.52	w	2.71	vw
4.42	w	2.66	vw
4.32	w	2.58	w
4.27	m	2.57	w
3.98	vw	2.56	w
3.92	w	2.52	vw
3.89	w	2.47	vw
3.87	w	2.45	vw
3.81	w	2.43	vw
3.74	m	2.40	vw
3.60	m	2.38	vw
3.55	m	2.31	vw

$\alpha 1$ = 1.54060 Å

DETD [0049] The product was analyzed using X-ray powder diffraction as described in Example 1, and the analyze gave the diffractogram depicted in FIG. 3 and given below in Table 3. Some additional peaks with low intensities found in the diffractogram have been omitted from Table 3.

TABLE 3

Positions and intensities of the major peaks in the XRP-diffractogram of the magnesium salt of **S-omeprazole** dihydrate, Form B.

d-value/Å	Relative Intensity
4.19	m
4.45	m
4.68	m
4.79	s
4.91	s
4.98	s
5.1	m
5.4	s
5.5	m
5.6	m
5.8	m
6.3	m
6.7	s
7.9	m
8.1	s
11.0	m
11.8	m
14.9	vs

DETD [0050] Conversion of Magnesium Salt of **S-omeprazole** Dehydrate to Trihydrate

DETD [0054] The product was analyzed using X-ray powder diffraction as described in Example 1 and gave the diffractogram depicted in FIG. 4 and given below in Table 4. Some additional peaks with low intensities found in the diffractogram have been omitted from Table 4.

TABLE 4

Positions and intensities of the major peaks in the XRP-diffractogram of the magnesium salt of **S-omeprazole** dihydrate, Form A.

d-value/Å	Relative Intensity
3.04	s
3.14	s
3.18	m

4.05	s
4.19	s
4.32	m
4.54	s
4.69	vs
5.2	s
5.3	s
5.8	s
6.2	vs
6.6	s
15.5	vs

CLM What is claimed is:

1. A process for the preparation of a potassium salt of **S-omeprazole**, which process comprises the following steps: a) oxidizing 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]thio]-1H-benzimidazole into **S-omeprazole** in an organic solvent; b) converting the **S-omeprazole** into the corresponding potassium salt of **S-omeprazole** by treating the **S-omeprazole** with a potassium source; and c) isolating the potassium salt of **S-omeprazole** thus obtained.

4. The process according to claim 1, wherein the obtained potassium salt of **S-omeprazole** is characterized by the following peaks in its X-ray powder diffractogram:

d-value/Å	Relative intensity	d-value/ (Å)	Relative intensity
13.6	vs	3.52	m
10.6	vw	3.42	w
7.8	m	3.38	w
6.8	m	3.34	m
6.5	m	3.28	w
6.2	w	3.20	m
6.1	m	3.12	w
5.8	s	3.06	w
5.4	m	3.03	w
5.3	w	2.97	w
5.2	w	2.93	vw
5.0	vw	2.89	w
4.75	m	2.85	m
4.71	w	2.76	w
4.52	w	2.71	vw
4.42	w	2.66	vw
4.32	w	2.58	w
4.27	m	2.57	w
3.98	vw	2.56	w
3.92	w	2.52	vw
3.89	w	2.47	vw
3.87	w	2.45	vw
3.81	w	2.43	vw
3.74	m	2.40	vw
3.60	m	2.38	vw
3.55	m	2.31	vw

$\alpha 1$ = 1.54060 Å

5. The potassium salt of **S-omeprazole**, wherein the compound is characterized by the following peaks in its X-ray powder

diffractogram:

d-value/Å	Relative intensity	d-value/ (Å)	Relative intensity
13.6	vs	3.52	m
10.6	vw	3.42	w
7.8	m	3.38	w
6.8	m	3.34	m
6.5	m	3.28	w
6.2	w	3.20	m
6.1	m	3.12	w
5.8	s	3.06	w
5.4	m	3.03	w
5.3	w	2.97	w
5.2	w	2.93	vw
5.0	vw	2.89	w
4.75	m	2.85	m
4.71	w	2.76	w
4.52	w	2.71	vw
4.42	w	2.66	vw
4.32	w	2.58	w
4.27	m	2.57	w
3.98	vw	2.56	w
3.92	w	2.52	vw
3.89	w	2.47	vw
3.87	w	2.45	vw
3.81	w	2.43	vw
3.74	m	2.40	vw
3.60	m	2.38	vw
3.55	m	2.31	vw

$\alpha 1$ = 1.54060 Å

6. A process for the preparation of the magnesium salt of **S-omeprazole** trihydrate, which comprises the following steps: a) mixing the potassium salt of **S-omeprazole** according to claim 5 with an organic solvent; b) converting the potassium salt of **S-omeprazole** into a corresponding magnesium salt of **S-omeprazole** by treating the potassium salt with a magnesium source; c) precipitating the magnesium salt of **S-omeprazole** by addition of a non-solvent; d) isolating the obtained magnesium salt of **S-omeprazole**; e) treating the obtained magnesium salt of **S-omeprazole** with water; and f) isolating and drying the obtained magnesium salt of **S-omeprazole** trihydrate.

9. The process according to claim 6 wherein steps a) to e) are replaced by the single step: converting the potassium salt of **S-omeprazole** into a corresponding magnesium salt of **S-omeprazole** by treating the potassium salt with a magnesium source in water.

11. The process according to claim 6 or 9, wherein the obtained magnesium salt of **S-omeprazole** trihydrate is characterized by the following major peaks in its X-ray powder diffractogram.

d-value/Å Relative Intensity

2.67	m
2.79	m
3.27	m
3.52	s
3.82	s
3.96	vs
4.14	m
5.2	m
5.6	m
6.7	vs
6.9	s
8.3	w
16.6	vs

L2 ANSWER 31 OF 42 USPATFULL on STN
ACCESSION NUMBER: 2002:221834 USPATFULL
TITLE: Substituted aryl compounds as novel cyclooxygenase-2 selective inhibitors, compositions and methods of use related applications
INVENTOR(S): Khanapure, Subhash P., Clinton, MA, UNITED STATES
Garvey, David S., Dover, MA, UNITED STATES
Earl, Richard A., Westford, MA, UNITED STATES
Ezawa, Maiko, Drummer Raod, MA, UNITED STATES
Fang, Xinqin, Lexington, MA, UNITED STATES
Gaston, Ricky D., Malden, MA, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002119977	A1	20020829	
	US 6706724	B2	20040316	
APPLICATION INFO.:	US 2001-24046	A1	20011221	(10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-256932P	20001221 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: EDWARD D GRIEFF, HALE & DORR LLP, 1455 PENNSYLVANIA AVE, NW, WASHINGTON, DC, 20004
NUMBER OF CLAIMS: 54
EXEMPLARY CLAIM: 1
LINE COUNT: 4855
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention describes novel substituted aryl compounds that are cyclooxygenase 2 (COX-2) selective inhibitors and novel compositions comprising at least one cyclooxygenase 2 (COX-2) selective inhibitor, and, optionally, at least one compound that donates, transfers or releases nitric oxide, stimulates endogenous synthesis of nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor or is a substrate for nitric oxide synthase, and/or, optionally, at least one therapeutic agent, such as, steroids, nonsterodal antiinflammatory compounds (NSAID), 5-lipoxygenase (5-LO) inhibitors, leukotriene B.sub.4 (LTB.sub.4) receptor antagonists, leukotriene A.sub.4 (LTA.sub.4) hydrolase inhibitors, 5-HT agonists, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) inhibitors, H.sub.2 antagonists, antineoplastic agents, antiplatelet agents, thrombin inhibitors, thromboxane inhibitors, decongestants, diuretics, sedating or non-sedating anti-histamines, inducible nitric oxide synthase inhibitors, opioids, analgesics, Helicobaxcter pylori inhibitors, proton pump inhibitors, isoprostane

inhibitors, and mixtures thereof. The invention also provides novel kits comprising at least one COX-2 selective inhibitor, and, optionally, at least one nitric oxide donor, and/or, optionally, at least one therapeutic agent. The novel cyclooxygenase 2 selective inhibitors of the invention can be optionally nitrosated and/or nitrosylated. The invention also provides methods for treating inflammation, pain and fever; for treating and/or improving the gastrointestinal properties of COX-2 selective inhibitors; for facilitating wound healing; for treating and/or preventing renal toxicity or other toxicities; for treating and/or preventing other disorders resulting from elevated levels of cyclooxygenase-2; and for improving the cardiovascular profile of COX-2 selective inhibitors.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM [0522] Suitable proton pump inhibitors, include, but are not limited to, omeprazole, **esomeprazole**, lansoprazole, rabeprazole, pantoprazole, and the like. Suitable proton pump inhibitors are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995, Pgs. 901-915; the Merck Index on CD-ROM, Twelfth Edition, Version 12:1, 1996; and in WO 00/50037 assigned to NitroMed Inc., the disclosures of which are incorporated herein by reference in their entirety.

DETD [0619] To acetic anhydride (0.460 mL) at 0° C. was added drop-wise, with stirring, fuming nitric acid (0.140 mL). This mixture was immediately added drop-wise to a solution of the product of Example 18b (0.43 mmol, 0.216 g) dissolved in ethyl acetate (5 mL), at 0° C. The resulting solution was stirred at 0° C. for 30 min, then quenched with water and neutralized with sodium carbonate. The organic layer was separated, dried over magnesium sulfate and filtered. The filtrate was evaporated under reduced pressure. Purification by silica gel column chromatography using ethyl acetate as the eluant gave the title compound as an **amorphous** glassy solid (0.217 g, 92% yield). .sup.1H NMR (300 MHz, CDCl.sub.3) δ7.95 (d, J=8.0 Hz, 2H), 7.39 (d, J=8.0 Hz, 2H), 6,88 (m, 3H), 6.61 (t, J=8.8 Hz, 1H), 6.43 (m, 2H), 4.79 (m, 2H), 4.61 (m, 3H), 4.28 (dd, J=7.3, 11.4 Hz, 1H), 3.83 (s, 2H), 3.12 (s, 3H); MS (APIMS) m/e 503 (M+HNO2).sup.+, 566 (M+18).sup.30 .

DETD [0621] To acetic anhydride (0.230 mL) at 0° C. was added drop-wise, with stirring, fuming nitric acid (0.07 mL). This mixture was immediately added drop-wise to a solution of the product of Example 19a (0.25 mmol, 0.112 g) dissolved in ethyl acetate, at 0° C. The resulting solution was stirred at 0° C. for 15 min, then quenched with water and neutralized with sodium carbonate. The organic layer was separated, dried over magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure. Purification by silica gel column chromatography using ethyl acetate as the eluant gave the title compound as an **amorphous** glassy solid, (69 mg, 56% yield). .sup.1H NMR (300 MHz, CDCl.sub.3) δ7.91 (d, J=8.3 Hz, 2H), 7.35 (d, J=8.3 Hz, 2H), 6.81 (s, 0.5H), 6.80 (s, 0.5H), 6.79 (s, 0.5H), 6.78 (s, 0.5H), 6.59 (tt, J=2.3, 9.0 Hz, 1H), 6.41 (s, 2H), 4.73 (m, 2H), 4.57 (m, 1H), 4.35 (m, 1H), 4.18 (dd, J=3.2, 6.2 Hz, 0.5H), 4.14 (dd, J=3.2, 6.2 Hz, 0.5H), 3.79 (s, 2H), 3.09 (s, 3H); MS (APIMS) m/e 509 (M+18).sup.+.

L2 ANSWER 32 OF 42 USPATFULL on STN
ACCESSION NUMBER: 2002:192160 USPATFULL
TITLE: ALKOXY SUBSTITUTED BENZIMIDAZOLE COMPOUNDS, PHARMACEUTICAL PREPARATIONS CONTAINING THE SAME, AND METHODS OF USING THE SAME
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Sancilio, Frederick D., Wilmington, NC, UNITED STATES

Stowell, Grayson Walker, Wilmington, NC, UNITED STATES
Jenkins, Douglas John, Wilmington, NC, UNITED STATES
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	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002103232	A1	20020801
	US 6444689	B2	20020903
APPLICATION INFO.:	US 2002-57659	A1	20020125 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2000-645145, filed on 24 Aug 2000, PATENTED Continuation-in-part of Ser. No. US 2000-516976, filed on 1 Mar 2000, PATENTED

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-150878P	19990826 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: MYERS BIGEL SIBLEY & SAJOVEC, PO BOX 37428, RALEIGH, NC, 27627
NUMBER OF CLAIMS: 64
EXEMPLARY CLAIM: 1
LINE COUNT: 4119

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compounds represented by formula (Ia) are disclosed by the invention, along with compositions and complexes thereof, optionally in combination with compounds of formula (Ib). Pharmaceutical formulations and methods of making and using such compounds are also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM [0010] The teachings regarding the methods of making omeprazole as referred to in these references, salts thereof, enantiomers thereof, and salts of the enantiomers, as well as formulations which may include these compounds, all rely on the chemical structure of omeprazole being accurately determined and the referenced compound or compounds being consistently prepared using the referenced techniques. More specifically, a methoxy group on the benzimidazole ring has been explicitly stated in the literature to be present at the 5-position, in omeprazole, a racemic mixture, and an optically pure isomer of omeprazole designated as **esomeprazole** or **s-omeprazole**. Applicants have now unexpectedly discovered the complexity of omeprazole and the relative bioactivity of each of its previously undiscovered and undisclosed attributes. More specifically, Applicants have confirmed that the methods of the prior art do not yield a single compound having the methoxy group in the 5-position on the benzimidazole ring as previously taught, nor do all of the methods of the prior art yield consistent results. In fact, omeprazole as conventionally referred to as a bulk drug substance (in its solid state) has been discovered to be present in the form of two pharmaceutically active compounds having the methoxy group on the benzimidazole ring at the 6- and 5-positions. Additionally, Applicants have discovered the presence of a second chiral location at the pyridine ring plane in each of the two compounds such that each compound has two positional isomers and four diastereomers. Therefore, the present invention provides these individual compounds, along with any salts, hydrates, solvates, combinations thereof, and polymorphs thereof, compositions of the above, and methods of making the same that are not taught or suggested by the prior art, pharmaceutical formulations of the compounds, compositions, and complexes of the present invention, and methods for using the same.

SUMM [0072] Accordingly, methods of the present invention provide for improved biological activity/efficacy (e.g. inhibition of gastric acid

secretions and, thus, treatment of gastric acid disturbances in mammals, including humans) of pharmaceutically active compounds omeprazole and **esomeprazole**, as presently known in the art, comprising administering to such mammals in need of treatment a non-toxic, therapeutically effective amount of any composition of the present invention comprising compounds or compositions of the present invention having individual diastereomers comprising S.sub.xa--R.sub.4q; S.sub.xa--R.sub.4z; S.sub.xb--R.sub.4q; or S.sub.xb--R.sub.4z, or one or more pharmaceutically acceptable salts, solvates, hydrates, or combinations thereof. Also provided are such methods wherein said compounds or complexes of the present invention having said selected individual diastereomer pair essentially free of compounds of the present invention having diastereomer pairs other than said selected individual diastereomers. A preferred diastereomer is S.sub.xa--R.sub.4q, and an especially preferred diastereomer is S.sub.xa--R.sub.4z.

SUMM [0080] In another aspect, the invention also provides compositions of active pharmaceutical ingredient ("API") comprising any of the compounds, compositions, or complexes of the present invention, each of which may be present in crystalline form, in part or in whole. Advantageously, each such compositions and/or complexes comprising compounds represented by formula (Ia) may also include any one or more of the specific compounds represented by formulae (Iai), (Iaii), (Iaiii), and (Iaiv), or pharmaceutically acceptable salts, solvates, hydrates, polymorphs, or combinations thereof, whether in crystalline form, **amorphous** form, or a combination thereof. Each can be used as the bases for any such API composition.

SUMM [0141] Any of such composition embodiments comprising any of the compounds represented by formulae (Ia) and (Ib), individual species of compounds (Iai)-(Ibi), (Iaii)-(Ibii), (Iaiii)-(Ibiii), and (Iaiv)-(Ibiv), diastereromers thereof, or one or more pharmaceutically acceptable salts, solvates, hydrates, or combinations thereof, may be present in crystalline form, **amorphous** form, or combinations thereof.

SUMM [0142] The invention also provides compositions of active pharmaceutical ingredient ("API") comprising any of the above composition embodiments. Advantageously, any of the compositions comprising compounds represented by formulae (Ia) and (Ib) may also comprise any of the specific compositions represented by formulae (Iai)-(Ibi); (Iaii)-(Ibii); (Iaiii)-(Ibiii); and (Iaiv)-(Ibiv) or one or more pharmaceutically acceptable salts, solvates, hydrates, polymorphs, or combinations thereof, whether in crystalline form, **amorphous** form, or a combination thereof, can be used in any such API compositions.

SUMM [0145] Additionally, when using such processes represented in the prior art, negligible or trace amounts of previously unknown compounds are formed as described herein. For example, in the preparation of such composition as referenced in the immediately preceding paragraph, compounds having the previously unknown diastereomers S.sub.xa--R.sub.4q and S.sub.xb--R.sub.4z are formed with varying and inconsistent ratios of compounds represented by formulae (Ia) and (Ib). Also formed in trace quantities, and typically in **amorphous** form, are compounds represented by formulae (Ia) and (Ib) having the previously unknown diastereomers S.sub.xa--R.sub.4z and S.sub.xb--R.sub.4q.

SUMM [0147] Accordingly, the processes taught in the prior art for the preparation of "omeprazole" as well as "**esomeprazole**" (the intended S-isomer of "omeprazole") provide quantities of previously unknown and unrecognized compounds having pharmaceutical activity, or

that are used as intermediates in the preparation of pharmaceutically active compounds of the present invention, or that are used as prodrugs that convert to the active metabolite in vivo. Furthermore, many such processes do not invariably provide the same result when conducted as taught in the prior art.

SUMM [0174] By employing the above method(s) of obtaining the compound represented by formula (Ia) in solid state, one obtains the (-) and (+) enantiomers as a racemic mixture, with these enantiomers including various amounts of diastereomers as set forth herein. In one embodiment, Applicants have discovered that the (-) and (+) enantiomers may be predominantly present as the S.sub.xa--R.sub.4q and S.sub.xb--R.sub.4z diastereomers respectively. Although not intending to be bound by theory, in this embodiment, the two molecules (i.e., compounds of formulae (Ia) and (Ib)) co-crystallize in a centric space group in which the molecules are related to each other through a center of inversion and linked by hydrogen bonding from the amine hydrogens to the sulfoxide oxygens. The R.sub.4 methoxy methyl is directed towards the center of the bridged complex. Examination of the contact distances in the region where the other methoxy methyl would presumably reside demonstrates that there is not adequate space within the lattice for the other diastereomers (S.sub.xa--R.sub.4z and S.sub.xb--R.sub.4q) to co-exist. In this embodiment, the compound represented by formula (Ia) may comprise about 99 percent (w/w) of the S.sub.xb--R.sub.4z and S.sub.xa--R.sub.4q diastereomers and the remaining percentage of other components which may include, for example, the diastereomers S.sub.xa--R.sub.4z and S.sub.xb--R.sub.4q, generally in **amorphous** form.

SUMM [0180] Although not intending to be bound by theory, such compounds of formula (Ia) are believed to be crystalline with little **amorphous** content. However, when grinding is applied to a solid sample comprising the compound of formula (Ia), and in a preferred embodiment the compounds of formulae (Ia) and (Ib), an increase in the **amorphous** character of the sample is believed to result along with an increase in the amount of compound of formula (Ib). Again, not intending to be bound by theory, it is believed that the sample undergoes a solid state transformation and "recrystallizes" or transforms over a relatively short period of time from the more **amorphous** state to a more crystalline state subsequent to grinding. Nonetheless, it is believed that by performing multiple grinding steps in sequence, (i.e., grinding followed by relaxation followed by grinding) one may obtain a solid sample that becomes more **amorphous** in character and hence comprises a greater amount of the compound of the formula (Ib) as opposed to a sample that has experienced a lesser amount of grinding.

SUMM [0182] The structure of the compound of formula (Ib) can be confirmed by solid state techniques such as, for example, X-ray powder diffraction patterns, Raman, FTIR, solid state NMR, and thermal analysis, of the ground material and the unground material. For example, comparison of the two powder patterns showed distinct decreases in intensity, broadening of the peaks, and an increase in the **amorphous** nature for the ground material. The ground material showed a powder pattern that is more consistent with the proposed more **amorphous** nature of the compound of formula (Ib), e.g., 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

DETD [0299] The following examples are intended to illustrate the invention, and are not to be construed as limiting the scope of the invention. For the purposes of the examples, the phrase "(5)6-methoxy 2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-

benzimidazole" refers to a combination of, preferably a co-crystallized mixture, (with or without an amount of **amorphous** compounds), of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole and 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole, each as determined and referenced herein.

L2 ANSWER 33 OF 42 USPATFULL on STN
ACCESSION NUMBER: 2002:75460 USPATFULL
TITLE: Alkoxy substituted benzimidazole compounds, pharmaceutical preparations containing the same, and methods of using the same
INVENTOR(S): Whittle, Robert R., 5006 Pine Needles Dr., Wilmington, NC, United States 28403
Sancilio, Frederick D., 2332 Ocean Point Dr., Wilmington, NC, United States 28405
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	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6369087	B1	20020409
APPLICATION INFO.:	US 2000-645145		20000824 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2000-519976, filed on 7 Mar 2000, now patented, Pat. No. US 6262085

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-150878P	19990826 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Reamer, James H.
LEGAL REPRESENTATIVE: Myers Bigel Sibley & Sajovec, Fontana, Esq., Steven A.
NUMBER OF CLAIMS: 68
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 0 Drawing Figure(s); 0 Drawing Page(s)
LINE COUNT: 4173
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Compounds represented by formula (Ia) are disclosed by the invention, along with compositions and complexes thereof, optionally in combination with compounds of formula (Ib). Pharmaceutical formulations and methods of making and using such compounds are also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM The teachings regarding the methods of making omeprazole as referred to in these references, salts thereof, enantiomers thereof, and salts of the enantiomers, as well as formulations which may include these compounds, all rely on the chemical structure of omeprazole being accurately determined and the referenced compound or compounds being consistently prepared using the referenced techniques. More specifically, a methoxy group on the benzimidazole ring has been explicitly stated in the literature to be present at the 5-position, in omeprazole, a racemic mixture, and an optically pure isomer of omeprazole designated as **esomeprazole** or **s-omeprazole**. Applicants have now unexpectedly discovered the complexity of omeprazole and the relative bioactivity of each of its previously undiscovered and undisclosed attributes. More specifically, Applicants have confirmed that the methods of the prior art do not yield

a single compound having the methoxy group in the 5-position on the benzimidazole ring as previously taught, nor do all of the methods of the prior art yield consistent results. In fact, omeprazole as conventionally referred to as a bulk drug substance (in its solid state) has been discovered to be present in the form of two pharmaceutically active compounds having the methoxy group on the benzimidazole ring at the 6- and 5-positions. Additionally, Applicants have discovered the presence of a second chiral location at the pyridine ring plane in each of the two compounds such that each compound has two positional isomers and four diastereomers. Therefore, the present invention provides these individual compounds, along with any salts, hydrates, solvates, combinations thereof, and polymorphs thereof, compositions of the above, and methods of making the same that are not taught or suggested by the prior art, pharmaceutical formulations of the compounds, compositions, and complexes of the present invention, and methods for using the same.

SUMM Accordingly, methods of the present invention provide for improved biological activity/efficacy (e.g. inhibition of gastric acid secretions and, thus, treatment of gastric acid disturbances in mammals, including humans) of pharmaceutically active compounds omeprazole and **esomeprazole**, as presently known in the art, comprising administering to such mammals in need of treatment a non-toxic, therapeutically effective amount of any composition of the present invention comprising compounds or compositions of the present invention having individual diastereomers comprising S.sub.xa-R.sub.4q; S.sub.xa-R.sub.4z; S.sub.xb-R.sub.4q; or S.sub.xb-R.sub.4z, or one or more pharmaceutically acceptable salts, solvates, hydrates, or combinations thereof. Also provided are such methods wherein said compounds or complexes of the present invention having said selected individual diastereomer pair essentially free of compounds of the present invention having diastereomer pairs other than said selected individual diastereomers. A preferred diastereomer is S.sub.xa-R.sub.4q, and an especially preferred diastereomer is S.sub.xa-R.sub.4z.

SUMM In another aspect, the invention also provides compositions of active pharmaceutical ingredient ("API") comprising any of the compounds, compositions, or complexes of the present invention, each of which may be present in crystalline form, in part or in whole. Advantageously, each such compositions and/or complexes comprising compounds represented by formula (Ia) may also include any one or more of the specific compounds represented by formulae (Iai), (Iaii), (laiii), and (Iaiv), or pharmaceutically acceptable salts, solvates, hydrates, polymorphs, or combinations thereof, whether in crystalline form, **amorphous** form, or a combination thereof. Each can be used as the bases for any such API composition.

SUMM Any of such composition embodiments comprising any of the compounds represented by formulae (Ia) and (Ib), individual species of compounds (Iai)-(Ibi), (Iaii)-(Ibii), (Iaiii)-(Ibiii), and (Iaiv)-(Ibiv), diastereromers thereof, or one or more pharmaceutically acceptable salts, solvates, hydrates, or combinations thereof, may be present in crystalline form, **amorphous** form, or combinations thereof.

SUMM The invention also provides compositions of active pharmaceutical ingredient ("API") comprising any of the above composition embodiments. Advantageously, any of the compositions comprising compounds represented by formulae (Ia) and (Ib) may also comprise any of the specific compositions represented by formulae (Iai)-(Ibi); (Iaii)-(Ibii); (Iaiii)-(Ibiii); and (Iaiv)-(Ibiv) or one or more pharmaceutically acceptable salts, solvates, hydrates, polymorphs, or combinations thereof, whether in crystalline form, **amorphous** form, or a combination thereof, can be used in any such API compositions.

SUMM Additionally, when using such processes represented in the prior art, negligible or trace amounts of previously unknown compounds are formed as described herein. For example, in the preparation of such composition as referenced in the immediately preceding paragraph, compounds having the previously unknown diastereomers S.sub.xa-R.sub.4q and S.sub.xb-R.sub.4z are formed with varying and inconsistent ratios of compounds represented by formulae (Ia) and (Ib). Also formed in trace quantities, and typically in **amorphous** form, are compounds represented by formulae (Ia) and (Ib) having the previously unknown diastereomers S.sub.xa-R.sub.4z and S.sub.xb-R.sub.4q.

SUMM Accordingly, the processes taught in the prior art for the preparation of "omeprazole" as well as "**esomeprazole**" (the intended S-isomer of "omeprazole") provide quantities of previously unknown and unrecognized compounds having pharmaceutical activity, or that are used as intermediates in the preparation of pharmaceutically active compounds of the present invention, or that are used as prodrugs that convert to the active metabolite in vivo. Furthermore, many such processes do not invariably provide the same result when conducted as taught in the prior art.

SUMM By employing the above method(s) of obtaining the compound represented by formula (Ia) in solid state, one obtains the (-) and (+) enantiomers as a racemic mixture, with these enantiomers including various amounts of diastereomers as set forth herein. In one embodiment, Applicants have discovered that the (-) and (+) enantiomers may be predominantly present as the S.sub.xa-R.sub.4q and S.sub.xb-R.sub.4z diastereomers respectively. Although not intending to be bound by theory, in this embodiment, the two molecules (i.e., compounds of formulae (Ia) and (Ib)) co-crystallize in a centric space group in which the molecules are related to each other through a center of inversion and linked by hydrogen bonding from the amine hydrogens to the sulfoxide oxygens. The R.sub.4 methoxy methyl is directed towards the center of the bridged complex. Examination of the contact distances in the region where the other methoxy methyl would presumably reside demonstrates that there is not adequate space within the lattice for the other diastereomers (S.sub.xa-R.sub.4z and S.sub.xb-R.sub.4q) to co-exist. In this embodiment, the compound represented by formula (Ia) may comprise about 99 percent (w/w) of the S.sub.xb-R.sub.4z and S.sub.xa-R.sub.4q diastereomers and the remaining percentage of other components which may include, for example, the diastereomers S.sub.xa-R.sub.4z and S.sub.xb-R.sub.4q, generally in **amorphous** form.

SUMM Although not intending to be bound by theory, such compounds of formula (Ia) are believed to be crystalline with little **amorphous** content. However, when grinding is applied to a solid sample comprising the compound of formula (Ia), and in a preferred embodiment the compounds of formulae (Ia) and (Ib), an increase in the **amorphous** character of the sample is believed to result along with an increase in the amount of compound of formula (Ib). Again, not intending to be bound by theory, it is believed that the sample undergoes a solid state transformation and "recrystallizes" or transforms over a relatively short period of time from the more **amorphous** state to a more crystalline state subsequent to grinding. Nonetheless, it is believed that by performing multiple grinding steps in sequence, (i.e., grinding followed by relaxation followed by grinding) one may obtain a solid sample that becomes more **amorphous** in character and hence comprises a greater amount of the compound of the formula (Ib) as opposed to a sample that has experienced a lesser amount of grinding.

SUMM The structure of the compound of formula (Ib) can be confirmed by solid state techniques such as, for example, X-ray powder diffraction patterns, Raman, FTIR, solid state NMR, and thermal analysis, of the ground material and the unground material. For example, comparison of the two powder patterns showed distinct decreases in intensity, broadening of the peaks, and an increase in the **amorphous** nature for the ground material. The ground material showed a powder pattern that is more consistent with the proposed more **amorphous** nature of the compound of formula (Ib), e.g., 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

DETD The following examples are intended to illustrate the invention, and are not to be construed as limiting the scope of the invention. For the purposes of the examples, the phrase "(5)6-methoxy 2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole" refers to a combination of, preferably a co-crystallized mixture, (with or without an amount of **amorphous** compounds), of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole and 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole, each as determined and referenced herein.

L2 ANSWER 34 OF 42 USPATFULL on STN

ACCESSION NUMBER:	2002:75458 USPATFULL		
TITLE:	Form of **S-omeprazole**		
INVENTOR(S):	Cotton, Hanna, Sodertalje, SWEDEN Kronstrom, Anders, Sodertalje, SWEDEN Mattson, Anders, Sodertalje, SWEDEN Moller, Eva, Sodertalje, SWEDEN		
PATENT ASSIGNEE(S):	AstraZeneca AB, Sodertalje, SWEDEN (non-U.S. corporation)		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6369085	B1	20020409
	WO 9854171		19981203
APPLICATION INFO.:	US 1998-77719		19980608 (9)
	WO 1998-SE974		19980505
			19980608 PCT 371 date
	NUMBER	DATE	
PRIORITY INFORMATION:	SE 1997-2065	19970530	
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	GRANTED		
PRIMARY EXAMINER:	Fan, Jane		
LEGAL REPRESENTATIVE:	White & Case LLP		
NUMBER OF CLAIMS:	12		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	5 Drawing Figure(s); 5 Drawing Page(s)		
LINE COUNT:	509		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to a novel form of the (-)-enantiomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole, i.e. **S-omeprazole**. More specifically, it relates to a novel form of the magnesium salt of the S-enantiomer of omeprazole trihydrate. The present invention also relates to processes for preparing such a form of the magnesium salt of **S-omeprazole** and pharmaceutical compositions containing it. Furthermore, the present invention also relates to new intermediates used in the process.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Form of **S-omeprazole**

AB The present invention relates to a novel form of the (-)-enantiomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole, i.e. **S-omeprazole**. More specifically, it relates to a novel form of the magnesium salt of the S-enantiomer of omeprazole trihydrate. The present invention also relates to processes for preparing such a form of the magnesium salt of **S-omeprazole** and pharmaceutical compositions containing it. Furthermore, the present invention also relates to new intermediates used in the process.

SUMM The present invention relates to a novel form of the (-)-enantiomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole, i.e. **S-omeprazole**. More specifically, it relates to a novel form of the magnesium salt of the S-enantiomer of omeprazole trihydrate. The present invention also relates to processes for preparing such a form of the magnesium salt of **S-omeprazole** and pharmaceutical compositions containing it. Furthermore, the present invention also relates to intermediates used in the process, and their preparation.

SUMM Omeprazole is a sulfoxide and a chiral compound, wherein the sulfur atom being the stereogenic center. Thus, omeprazole is a racemic mixture of its two single enantiomers, the R and S-enantiomer of omeprazole, herein referred to as R-omeprazole and **S-omeprazole.** The absolute configurations of the enantiomers of omeprazole have been determined by an X-ray study of an N-alkylated derivative of the (+)-enantiomer in non-salt form. The (+)-enantiomer of the non-salt form and the (-)-enantiomer of the non-salt form were found to have R and S configuration, respectively, and the (+)-enantiomer of the magnesium salt and the (-)-enantiomer of the magnesium salt were also found to have R and S configuration, respectively. The conditions for the optical rotation measurement for each of these enantiomers are described in WO 94/27988.

SUMM WO 96/02535 discloses a process for the preparation of the single enantiomers of omeprazole and salts thereof, and WO 96/01623 discloses a suitable tableted dosage forms of for instance magnesium salts of R- and **S-omeprazole.**

DRWD FIG. 1 shows a X-ray powder diffractogram of the magnesium salt of **S-omeprazole** trihydrate prepared according to the present invention.

DRWD FIG. 2 shows a X-ray powder diffractogram of the potassium salt of **S-omeprazole** prepared and used in the present application (See examples 2 and 3)

DRWD FIG. 3 shows a X-ray powder diffractogram of a magnesium salt of **S-omeprazole** dihyclrate prepared and used in the present application (See example 5)

DRWD FIG. 4 shows a X-ray powder diffractogram of a magnesium salt of **S-omeprazole** dihyclrate which is a polymorph of the dihydrate shown in FIG. 3 (See Example 6). This magnesium salt of **S-omeprazole** dihydrate has been prepared and can be used in the preparation of the magnesium salt of **S-omeprazole** trihydrate according to the present invention.

DRWD FIG. 5 shows X-ray powder diffractogram of the magnesium salt of **S-omeprazole** prepared according to example A in WO 96/01623.

DETD It has surprisingly been found that the magnesium salt of **S-omeprazole** occurs in a number of structurally different forms. It is an object of the present invention to provide a substantially pure magnesium salt of **S-omeprazole** trihydrate, hereinafter referred to as the compound of the invention. This

trihydrate can be obtained as a well defined compound. The present invention also provides a process to obtain and a method of differentiating the magnesium salt of **S-omeprazole** trihydrate from other forms of magnesium salts of **S-omeprazole.**

DETD The magnesium salt of **S-omeprazole** trihydrate obtained according to the present invention is substantially free from magnesium salts of R-omeprazole. The magnesium salt of **S-omeprazole** trihydrate obtained according to the present invention is also substantially free from other forms of magnesium salts of **S-omeprazole**, such as the corresponding magnesium salt compounds described in prior art, and dihydrates used in the preparation of the trihydrate compound according to the present invention.

DETD The compound of the invention is characterized by the positions and intensities of the major peaks in the X-ray powder diffractogram, but may also be characterized by conventional FT-IR spectroscopy. These characteristics are not exhibited by any other form of magnesium salt of **S-omeprazole** and accordingly, the magnesium salt of **S-omeprazole** trihydrate is easily distinguishable from any other crystal form of the magnesium salt of **S-omeprazole** disclosed in prior art. The compound of the invention is characterized by being highly crystalline, i.e. having a higher crystallinity than any other form of magnesium salt of **S-omeprazole** disclosed in the prior art. With the expression "any other form" is meant anhydrates, hydrates, solvates, and polymorphs or **amorphous** forms thereof disclosed in the prior art. Examples of any other forms of magnesium salt of **S-omeprazole** includes, but are not limited to, anhydrates, monohydrates, dihydrates, sesquihydrates, trihydrates, alcoholates, such as methanolates and ethanolates, and polymorphs or **amorphous** forms thereof.

DETD In a further aspect, the present invention provides processes for the preparation of the magnesium salt of **S-omeprazole** trihydrate which comprises;

DETD a) treating a magnesium salt of **S-omeprazole** of any form, for example prepared according to procedures known in the art such as Example A in WO 96/01623 which is incorporated herein by reference, with water at a suitable temperature for a suitable time. By a suitable temperature is meant a temperature which induces the transformation of starting material to product without decomposing any of these compounds. Examples of such suitable temperatures include, but are not limited to, room temperature and above. By a suitable time is meant a time that results in high conversion of the starting material into product without causing any decomposition of either compounds, i.e. results in a good yield. This suitable time will vary depending on the temperature used in a way well known to people in the art. The higher the temperature, the shorter time is needed to give the desired conversion. The amount of water is not crucial and will depend on the process conditions used. The magnesium salt of **S-omeprazole** trihydrate is thereafter separated from the aqueous slurry, for example by filtration or centrifugation and thereafter dried to constant weight; or

DETD The resulting potassium salt of **S-omeprazole** is thereafter converted to the corresponding magnesium salt by treatment with a magnesium source, such as magnesium sulfate in a lower alcohol, such as methanol. The solution is optionally filtered and the precipitation is initialized by addition of a non-solvent such as acetone. The product is filtered off and optionally washed with water and further processed as is described in a) above. Alternatively, the potassium salt may be treated with a magnesium source, such as magnesium sulfate in water, and isolation of the magnesium salt of **S-omeprazole** trihydrate, or any other conventional technique for transforming a potassium salt to the corresponding magnesium salt can be

used and is within the scope of the present invention.

DETD Yet a further aspect of the present invention is to provide a suitable intermediate used in the preparation of the compound of the invention, as well as a process for its preparation. The potassium salt of **S-omeprazole** is found to be such a suitable intermediate. The potassium salt of **S-omeprazole** may also be used as an active component of a pharmaceutical formulation to be used in the treatment of gastrointestinal diseases.

DETD The compound of the invention, i.e. the magnesium salt of **S-omeprazole** trihydrate, prepared according to the present invention may be analyzed by XRPD, a technique which is known per se.

DETD The amount of water in the magnesium salt of **S-omeprazole** trihydrate is determined by thermogravimetric analysis, a technique which is known per se.

DETD Any suitable route of administration may be employed for providing the patient with an effective dosage of the magnesium salt of **S-omeprazole** trihydrate, according to the invention. For example, peroral or parental formulations and the like may be employed. Dosage forms include capsules, tablets, dispersions, suspensions and the like.

DETD It is further provided a pharmaceutical composition comprising the magnesium salt of **S-omeprazole** trihydrate according to the invention, as active ingredient, in association with a pharmaceutically acceptable carrier, diluent or excipient and optionally other therapeutic ingredients. Compositions comprising other therapeutic ingredients are especially of interest in the treatment of Helicobacter infections. The invention also provides the use of the magnesium salt of **S-omeprazole** trihydrate of the invention in the manufacture of a medicament for use in the treatment of a gastric-acid related condition and a method of treating a gastric-acid related condition which method comprises administering to a subject suffering from said condition a therapeutically effective amount of the magnesium salt of **S-omeprazole** trihydrate according to the invention.

DETD In the practice of the invention, the most suitable route of administration as well as the magnitude of a therapeutic dose of the magnesium salt of **S-omeprazole** trihydrate according to the invention in any given case will depend on the nature and severity of the disease to be treated. The dose, and dose frequency, may also vary according to the age, body weight, and response of the individual patient. Special requirements may be needed for patients having Zollinger-Ellison syndrome, such as a need for higher doses than the average patient. Children and patients with liver diseases generally will benefit from doses that are somewhat lower than the average. Thus, in some conditions it may be necessary to use doses outside the ranges stated below, for example long term treatments may request lower dosage. Such higher and lower doses are within the scope of the present invention. Such daily doses may vary between 5 mg to 300 mg.

DETD Combination preparations comprising the magnesium salt of **S-omeprazole** trihydrate and other active ingredients may also be used. Examples of such active ingredients include, but are not limited to anti-bacterial compounds, non-steroidal anti-inflammatory agents, antacid agents, alginates and prokinetic agents.

DETD Water (157 kg) was added to the wet crystals of the magnesium salt of **S-omeprazole**, prepared according to Example 4, below. The mixture was heated to 38° C. with stirring and left for 3 hours. The crystals were filtered off and dried in vacuo. Yield: 31.6 kg

DETD

TABLE 1

Positions and intensities of the major peaks in the XRP-diffractogram of the magnesium salt of **S-omeprazole** trihydrate.

d-value / Å	Relative Intensity

2.67 m
2.79 m
3.27 m
3.52 s
3.82 s
3.96 vs
4.14 m
5.2 m
5.6 m
6.7 vs
6.9 s
8.3 w
16.6 vs
DETD
TABLE 2

Positions and intensities of the major peaks in the XRP-diffractogram of the potassium salt of **S-omeprazole.**

d-value/Å	Relative intensity	d-value (Å)	Relative intensity
13.6	vs	3.52	m
10.6	vw	3.42	w
7.8	m	3.38	w
6.8	m	3.34	m
6.5	m	3.28	w
6.2	w	3.20	m
6.1	m	3.12	w
5.8	s	3.06	w
5.4	m	3.03	w
5.3	w	2.97	w $\alpha 1$ = 1.54060 Å
5.2	w	2.93	vw
5.0	vw	2.89	w
4.75	m	2.85	m
4.71	w	2.76	w
4.52	w	2.71	vw
4.42	w	2.66	vw
4.32	w	2.58	w
4.27	m	2.57	w
3.98	vw	2.56	w
3.92	w	2.52	vw
3.89	w	2.47	vw
3.87	w	2.45	vw
3.81	w	2.43	vw
3.74	m	2.40	vw
3.60	m	2.38	vw
3.55	m	2.31	vw

DETD
TABLE 3

Positions and intensities of the major peaks in the XRP-diffractogram of the magnesium salt of **S-omeprazole** dihydrate, Form B.

d-value/Å	Relative Intensity
4.19	m
4.45	m
4.68	m
4.79	s
4.91	s
4.98	s
5.1	m

5.4 s
5.5 m
5.6 m
5.8 m
6.3 m
6.7 s
7.9 m
8.1 s
11.0 m
11.8 m
14.9 vs

DETD Convertion of magnesium salt of **S-omeprazole** dihydrate to trihydrate

DETD

TABLE 4

Positions and intensities of the major peaks in the XRP-diffractogram of the magnesium salt of **S-omeprazole** dihydrate, Form A.

d-value/Å Relative Intensity

3.04 s
3.14 s
3.18 m
4.05 s
4.19 s
4.32 m
4.54 s
4.69 vs
5.2 s
5.3 s
5.8 s
6.2 vs
6.6 s
15.5 vs

CLM What is claimed is:

1. The magnesium salt of **S-omeprazole** trihydrate, wherein the compound is characterized by the following major peaks in its X-ray diffractogram:

d-value / Å Relative Intensity

2.67 m
2.79 m
3.27 m
3.52 s
3.82 s
3.96 vs
4.14 m
5.2 m
5.6 m
6.7 vs
6.9 s
8.3 w
16.6 vs

2. The magnesium salt of **S-omeprazole** trihydrate according to claim 1, wherein the compound is in a highly crystalline form.

3. The magnesium salt of **S-omeprazole** trihydrate according to claim 1, wherein the compound is in a stable form.

4. A process for the preparation of the magnesium salt of **S-omeprazole** trihydrate according to any of claims 1, 2 or 3 which comprises treating a magnesium salt of **S-omeprazole** any other form with water.

5. A process for the preparation of the magnesium salt of **S-omeprazole** trihydrate according to any of claims 1, 2 or 3 which comprises the following steps: a) mixing a potassium salt of **S-omeprazole** with an organic solvent; b) converting the potassium salt of **S-omeprazole** into a corresponding magnesium salt of **S-omeprazole** by treating the potassium salt with a magnesium source; c) precipitating the magnesium salt of **S-omeprazole** by addition of a non-solvent; d) isolating the obtained magnesium salt of **S-omeprazole**; e) treating the obtained magnesium salt of **S-omeprazole** with water, and f) isolating and drying the obtained magnesium salt of **S-omeprazole** trihydrate.

8. The process according to claim 5 wherein steps a) to e) are replaced by the following single step: converting the potassium salt of **S-omeprazole** into a corresponding magnesium salt of **S-omeprazole** by treating the potassium salt with a magnesium source in water.

11. A pharmaceutical composition comprising the magnesium salt of **S-omeprazole** trihydrate according to any of claims 1, 2 or 3 as active ingredient and a pharmaceutically acceptable carrier.

12. A method of treating a gastric acid related condition which method comprises administering to a subject suffering from said condition a therapeutically effective amount of the magnesium salt of **S-omeprazole** trihydrate according to any of claims 1, 2 or 3.

L2 ANSWER 35 OF 42 USPATFULL on STN

ACCESSION NUMBER: 2001:221062 USPATFULL

TITLE: Dry blend pharmaceutical unit dosage form

INVENTOR(S): Whittle, Robert R., 5006 Pine Needles Dr., Wilmington, NC, United States 28403
Sancilio, Frederick D., 2332 Ocean Point Dr., Wilmington, NC, United States 28405
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Jenkins, Douglas John, 6400 Purple Martin Ct., Wilmington, NC, United States 28411-8323
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	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6326384	B1	20011204
APPLICATION INFO.:	US 2000-645148		20000824 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2000-519976, filed on 7 Mar 2000, now patented, Pat. No. US 6262085

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-150878P	19990826 (60)

DOCUMENT TYPE: Utility

FILE SEGMENT: GRANTED

PRIMARY EXAMINER: Reamer, James H.

LEGAL REPRESENTATIVE: Myers Bigel Sibley Sajovec P.A., Fontana, Esq., Steven A.
NUMBER OF CLAIMS: 16
EXEMPLARY CLAIM: 1
LINE COUNT: 3884
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides dry blend pharmaceutical formulations in unit dosage forms comprising per dosage unit one or more active pharmaceutical ingredients or pharmaceutically acceptable salts, solvates, hydrates, or combinations thereof wherein the ratio of said one or more active pharmaceutical ingredients in said formulations is essentially the same as the ratio of said active pharmaceutical ingredients in the corresponding, non-formulated drug substance and, wherein said formulations in unit dosage form are adapted for oral administration.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM The teachings regarding the methods of making omeprazole as referred to in these references, salts thereof, enantiomers thereof, and salts of the enantiomers, as well as formulations which may include these compounds, all rely on the chemical structure of omeprazole being accurately determined and the referenced compound or compounds being consistently prepared using the referenced techniques. More specifically, a methoxy group on the benzimidazole ring has been explicitly stated in the literature to be present at the 5-position, in omeprazole, a racemic mixture, and an optically pure isomer of omeprazole designated as **esomeprazole** or **s-omeprazole**. Applicants have now unexpectedly discovered the complexity of omeprazole and the relative bioactivity of each of its previously undiscovered and undisclosed attributes. More specifically, Applicants have confirmed that the methods of the prior art do not yield a single compound having the methoxy group in the 5-position on the benzimidazole ring as previously taught, nor do all of the methods of the prior art yield consistent results. In fact, omeprazole as conventionally referred to as a bulk drug substance (in its solid state) has been discovered to be present in the form of two pharmaceutically active compounds having the methoxy group on the benzimidazole ring at the 6- and 5-positions. Additionally, Applicants have discovered the presence of a second chiral location at the pyridine ring plane in each of the two compounds such that each compound has two positional isomers and four diastereomers. Therefore, the present invention provides these individual compounds, along with any salts, hydrates, solvates, combinations thereof, and polymorphs thereof, compositions of the above, and methods of making the same that are not taught or suggested by the prior art, pharmaceutical formulations of the compounds, compositions, and complexes of the present invention, and methods for using the same.

SUMM Accordingly, methods of the present invention provide for improved biological activitylefficacy (e.g. inhibition of gastric acid secretions and, thus, treatment of gastric acid disturbances in mammals, including humans) of pharmaceutically active compounds omeprazole and **esomeprazole**, as presently known in the art, comprising administering to such mammals in need of treatment a non-toxic, therapeutically effective amount of any composition of the present invention comprising compounds or compositions of the present invention having individual diastereomers comprising S.sub.xa -R.sub.4q ; S.sub.xa -R.sub.4z ; S.sub.xb -R.sub.4q ; or S.sub.xb -R.sub.4z, or one or more pharmaceutically acceptable salts, solvates, hydrates, or combinations thereof. Also provided are such methods wherein said compounds or complexes of the present invention having said selected individual diastereomer pair essentially free of compounds of the present invention having diastereomer pairs other than said selected individual

diastereomers. A preferred diastereomer is S.sub.xa -R.sub.4q, and an especially preferred diastereomer is S.sub.xa -R.sub.4z.

SUMM In another aspect, the invention also provides compositions of active pharmaceutical ingredient ("API") comprising any of the compounds, compositions, or complexes of the present invention, each of which may be present in crystalline form, in part or in whole. Advantageously, each such compositions and/or complexes comprising compounds represented by formula (Ia) may also include any one or more of the specific compounds represented by formulae (Iai), (Iaii), (Iaiii), and (Iaiv), or pharmaceutically acceptable salts, solvates, hydrates, polymorphs, or combinations thereof, whether in crystalline form, **amorphous** form, or a combination thereof. Each can be used as the bases for any such API composition.

SUMM Any of such composition embodiments comprising any of the compounds represented by formulae (Ia) and (Ib), individual species of compounds (Iai)-(Ibi), (Iaii)-(Ibii), (Iaiii)-(Ibiii), and (Iaiv)-(Ibiv), diastereromers thereof, or one or more pharmaceutically acceptable salts, solvates, hydrates, or combinations thereof, may be present in crystalline form, **amorphous** form, or combinations thereof.

SUMM The invention also provides compositions of active pharmaceutical ingredient ("API") comprising any of the above composition embodiments. Advantageously, any of the compositions comprising compounds represented by formulae (Ia) and (Ib) may also comprise any of the specific compositions represented by formulae (Iai)-(Ibi); (Iaii)-(Ibii); (Iaiii)-(Ibiii); and (Iaiv)-(Ibiv) or one or more pharmaceutically acceptable salts, solvates, hydrates, polymorphs, or combinations thereof, whether in crystalline form, **amorphous** form, or a combination thereof, can be used in any such API compositions.

SUMM Additionally, when using such processes represented in the prior art, negligible or trace amounts of previously unknown compounds are formed as described herein. For example, in the preparation of such composition as referenced in the immediately preceding paragraph, compounds having the previously unknown diastereomers S.sub.xa -R.sub.4q and S.sub.xb -R.sub.4z are formed with varying and inconsistent ratios of compounds represented by formulae (Ia) and (Ib). Also formed in trace quantities, and typically in **amorphous** form, are compounds represented by formulae (Ia) and (Ib) having the previously unknown diastereomers S.sub.xa -R.sub.4z and S.sub.xb -R.sub.4q.

SUMM Accordingly, the processes taught in the prior art for the preparation of "omeprazole" as well as "**esomeprazole**" (the intended S-isomer of "omeprazole") provide quantities of previously unknown and unrecognized compounds having pharmaceutical activity, or that are used as intermediates in the preparation of pharmaceutically active compounds of the present invention, or that are used as prodrugs that convert to the active metabolite in vivo. Furthermore, many such processes do not invariably provide the same result when conducted as taught in the prior art.

SUMM By employing the above method(s) of obtaining the compound represented by formula (Ia) in solid state, one obtains the (-) and (+) enantiomers as a racemic mixture, with these enantiomers including various amounts of diastereomers as set forth herein. In one embodiment, Applicants have discovered that the (-) and (+) enantiomers may be predominantly present as the S.sub.xa -R.sub.4q and S.sub.xb -R.sub.4z diastereomers respectively. Although not intending to be bound by theory, in this embodiment, the two molecules (i.e., compounds of formulae (Ia) and (Ib)) co-crystallize in a centric space group in which the molecules are

related to each other through a center of inversion and linked by hydrogen bonding from the amine hydrogens to the sulfoxide oxygens. The R.sub.4 methoxy methyl is directed towards the center of the bridged complex. Examination of the contact distances in the region where the other methoxy methyl would presumably reside demonstrates that there is not adequate space within the lattice for the other diastereomers (S.sub.xa -R.sub.4z and S.sub.xb -R.sub.4q) to co-exist. In this embodiment, the compound represented by formula (Ia) may comprise about 99 percent (w/w) of the S.sub.xb -R.sub.4z and S.sub.xa -R.sub.4q diastereomers and the remaining percentage of other components which may include, for example, the diastereomers S.sub.xa -R.sub.4z and S.sub.xb -R.sub.4q, generally in **amorphous** form.

SUMM Although not intending to be bound by theory, such compounds of formula (Ia) are believed to be crystalline with little **amorphous** content. However, when grinding is applied to a solid sample comprising the compound of formula (Ia), and in a preferred embodiment the compounds of formulae (Ia) and (Ib), an increase in the **amorphous** character of the sample is believed to result along with an increase in the amount of compound of formula (Ib). Again, not intending to be bound by theory, it is believed that the sample undergoes a solid state transformation and "recrystallizes" or transforms over a relatively short period of time from the more **amorphous** state to a more crystalline state subsequent to grinding. Nonetheless, it is believed that by performing multiple grinding steps in sequence, (i.e., grinding followed by relaxation followed by grinding) one may obtain a solid sample that becomes more **amorphous** in character and hence comprises a greater amount of the compound of the formula (Ib) as opposed to a sample that has experienced a lesser amount of grinding.

SUMM The structure of the compound of formula (Ib) can be confirmed by solid state techniques such as, for example, X-ray powder diffraction patterns, Raman, FTIR, solid state NMR, and thermal analysis, of the ground material and the unground material. For example, comparison of the two powder patterns showed distinct decreases in intensity, broadening of the peaks, and an increase in the **amorphous** nature for the ground material. The ground material showed a powder pattern that is more consistent with the proposed more **amorphous** nature of the compound of formula (Ib), e.g., 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

DETD The following examples are intended to illustrate the invention, and are not to be construed as limiting the scope of the invention. For the purposes of the examples, the phrase "(5)6-methoxy 2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole" refers to a combination of, preferably a co-crystallized mixture, (with or without an amount of **amorphous** compounds), of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole and 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole, each as determined and referenced herein.

L2 ANSWER 36 OF 42 USPATFULL on STN
ACCESSION NUMBER: 2001:202216 USPATFULL
TITLE: Pharmaceutical formulations
INVENTOR(S): Whittle, Robert R., 5006 Pine Needles Dr., Wilmington, NC, United States 28403
Sancilio, Frederick D., 2332 Ocean Point Dr., Wilmington, NC, United States 28405
Stowell, Grayson Walker, 710 Darwin Dr., Wilmington, NC, United States 28405
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Whittall, Linda B., 2204 Splitbrook Ct., Wilmington, NC, United States 28411
Meyer, Glenn Alan, 6117 Clairidge Rd., Wilmington, NC, United States 28403

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6316020	B1	20011113
APPLICATION INFO.:	US 2000-629587		20000731 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2000-519976, filed on 7 Mar 2000, now patented, Pat. No. US 6202085

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-150878P	19990826 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Reamer, James H.
LEGAL REPRESENTATIVE: Myers Bigel Sibley & Sajovec, P.A., Fontana, Esq., Steven A.
NUMBER OF CLAIMS: 15
EXEMPLARY CLAIM: 1
LINE COUNT: 3523

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Pharmaceutical compositions and formulations comprised of one or more active ingredients or pharmaceutically acceptable salts, solvates, hydrates, or combinations thereof combined with at least one cyclodextrin.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM The teachings regarding the methods of making omeprazole as referred to in these references, salts thereof, enantiomers thereof, and salts of the enantiomers, as well as formulations which may include these compounds, all rely on the chemical structure of omeprazole being accurately determined and the referenced compound or compounds being consistently prepared using the referenced techniques. More specifically, a methoxy group on the benzimidazole ring has been explicitly stated in the literature to be present at the 5-position, in omeprazole, a racemic mixture, and an optically pure isomer of omeprazole designated as **esomeprazole** or **s-omeprazole**. Applicants have now unexpectedly discovered that the complexity of omeprazole and the intricacies of the bioactivity of each of its previously undiscovered attributes has never been disclosed. More specifically, Applicants have confirmed that the methods of the prior art do not yield a single compound having the methoxy group in the 5-position on the benzimidazole ring as previously taught, nor do all of the methods of the prior art yield consistent results. In fact, omeprazole as conventionally referred to as a bulk drug substance (in its solid state) is confirmed to be present in the form of two pharmaceutically active compounds having the methoxy group on the benzimidazole ring at the 6- and 5-positions. Additionally, Applicants have discovered the presence of a second chiral location at the pyridine ring plane in each of the two compounds such that each compound has two positional isomers and four diastereomers. Therefore, the present invention provides these individual compounds, along with any salts, hydrates, solvates, combinations thereof, and polymorphs thereof, compositions of the above, and methods of making the same that are not taught or suggested by the prior art.

SUMM The present invention generally provides compounds represented by formula (Ia), co-crystallized compositions of compounds represented by

formulae (Ia) and (Ib) (as well as the potential presence of **amorphous** compound, typically of compounds represented by formula (1b), the presence or amount of which can increase as the percent of such (1b) compounds increases), each described in detail herein, one or more pharmaceutically acceptable salts, solvates, hydrates, or combinations thereof, and complexes thereof. Diastereomers of the above are also provided. The invention also provides compositions and pharmaceutical formulations of the above. Methods of making the above are also provided by the present invention.

SUMM Accordingly, methods of the present invention provide for improved biological activity/efficacy (e.g. inhibition of gastric acid secretions and treatment of gastric acid disturbances in mammals, including humans) of pharmaceutically active compounds omeprazole and **esomeprazole** , as presently known in the art, comprising administering to such mammals in need of treatment a non-toxic, therapeutically effective amount of any composition of the present invention comprising compounds or compositions of the present invention having individual diastereomers comprising S.sub.xa --R.sub.4q ; S.sub.xa --R.sub.4z ; S.sub.xb --R.sub.4q ; or S.sub.xb --R.sub.4z, or pharmaceutically acceptable salts, solvates, hydrates, or combinations thereof. Also provided are such methods wherein said compounds or complexes of the present invention having said selected individual diastereomer pair essentially free of compounds of the present invention having diastereomer pairs other than said selected individual diastereomers. A preferred diastereomer is S.sub.xa --R.sub.4q, and an especially preferred diastereomer is S.sub.xa --R.sub.4z.

SUMM In another aspect, the invention also provides a composition of active pharmaceutical ingredient ("API") comprising any of the above composition embodiments, each of which may be present in crystalline form. Advantageously, any of the compositions comprising compounds represented by formula (Ia) may also comprise any of the specific compounds represented by formulae (Iai), (Iaii), (Iaiii), and (Iaiv), or pharmaceutically acceptable salts, solvates, hydrates, polymorphs, or combinations thereof whether in crystalline form, **amorphous** form, or a combination thereof, can be used in any such API composition.

SUMM The invention also provides compositions of active pharmaceutical ingredient ("API") comprising any of the above composition embodiments. Advantageously, any of the compositions comprising compounds represented by formulae (Ia) and (Ib) may also comprise any of the specific compositions represented by formulae (Iai)-(Ibi); (Iaii)-(Ibii); (Iaiii)-(Ibiii); and (Iaiv)-(Ibiv) or pharmaceutically acceptable salts, solvates, hydrates, polymorphs, or combinations thereof, whether in crystalline form, **amorphous** form, or a combination thereof, can be used in any such API compositions.

SUMM Additionally, when using such process represented in the prior art, negligible or trace amounts of previously unknown compounds are formed as described herein. For example, in the preparation of such composition as referenced in the immediately preceding paragraph, compounds having the previously unknown diastereomers S.sub.xa --R.sub.4q and S.sub.xb --R.sub.4z are formed with varying and inconsistent ratios of compounds represented by formulae (Ia) and (Ib). Also formed in trace quantities, and typically in **amorphous** form, are compounds represented by formulae (Ia) and (Ib) having the previously unknown diastereomers S.sub.xa --R.sub.4z and S.sub.xb --R.sub.4q.

SUMM Accordingly, the processes taught in the prior art for the preparation of "omeprazole" as well as "**esomeprazole**" (the intended S-isomer of "omeprazole") provide quantities of previously unknown and

unrecognized compounds having pharmaceutical activity, or which are used as intermediates in the preparation of pharmaceutically active compounds of the present invention, or which are used as predrugs which convert to the active metabolite in vivo. Furthermore, many such processes do not invariably provide the same result when conducted as taught in the prior art.

SUMM By employing the above method(s) of obtaining the compound represented by formula (Ia) in solid state, one obtains the (-) and (+) enantiomers as a racemic mixture, with these enantiomers including various amounts of diastereomers as set forth herein. In one embodiment, Applicants have discovered that the (-) and (+) enantiomers may be predominantly present as the S--S and R--R diastereomers respectively. Although not intending to be bound by theory, in this embodiment, the two molecules (i.e., compounds of formulae (Ia) and (Ib)) co-crystallize in a centric space group in which the molecules are related to each other through a center of inversion and linked by hydrogen bonding from the amine hydrogens to the sulfoxide oxygens. The R.sub.4 methoxy methyl is directed towards the center of the bridged complex. Examination of the contact distances in the region where the other methoxy methyl would presumably reside demonstrates that there is not adequate space within the lattice for the other diastereomers (S--R and R--S) to co-exist. In this embodiment, the compound represented by formula (Ia) may comprise about 99 percent (w/w) of the R--R and S--S diastereomers and the remaining percentage of other components which may include, for example, the diastereomers S--R and R--S, generally in **amorphous** form.

SUMM Although not intending to be bound by theory, such compounds of formula (Ia) are believed to be crystalline with little **amorphous** content. However, when grinding is applied to a solid sample comprising the compound of formulae (Ia), and in a preferred embodiment the compounds of formulae (Ia) and (Ib), an increase in the **amorphous** character of the sample is believed to result along with an increase in the amount of compound of formula (Ib). Again, not intending to be bound by theory, it is believed that the sample undergoes a solid state transformation and "recrystallizes" or transforms over a relatively short period of time from the more **amorphous** state to a more crystalline state subsequent to grinding. Nonetheless, it is believed that by performing multiple grinding steps in sequence, (i.e., grinding followed by relaxation followed by grinding) one may obtain a solid sample that becomes more **amorphous** in character and hence comprises a greater amount of the compound of the formula (Ib) as opposed to a sample that has experienced a lower amount of grinding.

SUMM The structure of the compound of formula (Ib) can be confirmed by solid state techniques such as, for example, X-ray powder diffraction patterns, Raman, FTIR, solid state NMR, and thermal analysis, of the ground material and the unground material. For example, comparison of the two powder patterns showed distinct decreases in intensity, broadening of the peaks, and an increase in the **amorphous** nature for the ground material. The ground material showed a powder pattern that is more consistent with the proposed more **amorphous** nature of the compound of formula (Ib), e.g., 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

DETD The following examples are intended to illustrate the invention, and are not to be construed as limiting the scope of the invention. For the purposes of the examples, the phrase "(5)6-methoxy 2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole" refers to a co-crystallized mixture, (with or without an amount of **amorphous** compounds), of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-

methyl]sulfinyl]-1H-benzimidazole and 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole, each as determined and referenced herein.

L2 ANSWER 37 OF 42 USPATFULL on STN
ACCESSION NUMBER: 2001:196631 USPATFULL
TITLE: Pharmaceutical unit dosage form
INVENTOR(S): Whittle, Robert R., 5006 Pine Needles Dr., Wilmington, NC, United States 28403
Sancilio, Frederick D., 2332 Ocean Point Dr., Wilmington, NC, United States 28405
Stowell, Grayson Walker, 710 Darwin Dr., Wilmington, NC, United States 28405
Jenkins, Douglas John, 6400 Purple Martin Ct., Wilmington, NC, United States 28411-8323
Whittall, Linda B., 2204 Splitbrook Ct., Wilmington, NC, United States 28411
Meyer, Glenn Alan, 6117 Clairidge Rd., Wilmington, NC, United States 28403
Fontana, Steven A., 5344 Beretta Way, Wilmington, NC, United States 28409

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6312723	B1	20011106
APPLICATION INFO.:	US 2000-629634		20000731 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2000-519976, filed on 7 Mar 2000, now patented, Pat. No. US 6262085

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-150878P	19990826 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Reamer, James H.
LEGAL REPRESENTATIVE: Myers Bigel Sibley & Sajovec, P.A., Fontana, Esq., Steven A.
NUMBER OF CLAIMS: 12
EXEMPLARY CLAIM: 1
LINE COUNT: 3517
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Pharmaceutical formulations, in oral unit dosage forms, have one or more active ingredients or pharmaceutically acceptable salts, solvates, hydrates, or combinations thereof combined with at least one cyclodextrin.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM The teachings regarding the methods of making omeprazole as referred to in these references, salts thereof, enantiomers thereof, and salts of the enantiomers, as well as formulations which may include these compounds, all rely on the chemical structure of omeprazole being accurately determined and the referenced compound or compounds being consistently prepared using the referenced techniques. More specifically, a methoxy group on the benzimidazole ring has been explicitly stated in the literature to be present at the 5-position, in omeprazole, a racemic mixture, and an optically pure isomer of omeprazole designated as **esomeprazole** or **s-omeprazole**. Applicants have now unexpectedly discovered that the complexity of omeprazole and the intricacies of the bioactivity of each of its previously undiscovered attributes has never been disclosed. More specifically, Applicants have confirmed that the methods of the prior art do not yield a single compound having the methoxy group in the

5-position on the benzimidazole ring as previously taught, nor do all of the methods of the prior art yield consistent results. In fact, omeprazole as conventionally referred to as a bulk drug substance (in its solid state) is confirmed to be present in the form of two pharmaceutically active compounds having the methoxy group on the benzimidazole ring at the 6- and 5-positions. Additionally, Applicants have discovered the presence of a second chiral location at the pyridine ring plane in each of the two compounds such that each compound has two positional isomers and four diastereomers. Therefore, the present invention provides these individual compounds, along with any salts, hydrates, solvates, combinations thereof, and polymorphs thereof, compositions of the above, and methods of making the same that are not taught or suggested by the prior art.

SUMM The present invention generally provides compounds represented by formula (Ia), co-crystallized compositions of compounds represented by formulae (Ia) and (Ib) (as well as the potential presence of **amorphous** compound, typically of compounds represented by formula (1b), the presence or amount of which can increase as the percent of such (1b) compounds increases), each described in detail herein, one or more pharmaceutically acceptable salts, solvates, hydrates, or combinations thereof, and complexes thereof. Diastereomers of the above are also provided. The invention also provides compositions and pharmaceutical formulations of the above. Methods of making the above are also provided by the present invention.

SUMM Accordingly, methods of the present invention provide for improved biological activity/efficacy (e.g. inhibition of gastric acid secretions and treatment of gastric acid disturbances in mammals, including humans) of pharmaceutically active compounds omeprazole and **esomeprazole** , as presently known in the art, comprising administering to such mammals in need of treatment a non-toxic, therapeutically effective amount of any composition of the present invention comprising compounds or compositions of the present invention having individual diastereomers comprising S.sub.xa --R.sub.4q ; S.sub.xa --R.sub.4z ; S.sub.xb --R.sub.4q ; or S.sub.xb --R.sub.4z, or pharmaceutically acceptable salts, solvates, hydrates, or combinations thereof. Also provided are such methods wherein said compounds or complexes of the present invention having said selected individual diastereomer pair essentially free of compounds of the present invention having diastereomer pairs other than said selected individual diastereomers. A preferred diastereomer is S.sub.xa --R.sub.4q, and an especially preferred diastereomer is S.sub.xa --R.sub.4z.

SUMM In another aspect, the invention also provides a composition of active pharmaceutical ingredient ("API") comprising any of the above composition embodiments, each of which may be present in crystalline form. Advantageously, any of the compositions comprising compounds represented by formula (Ia) may also comprise any of the specific compounds represented by formulae (Iai), (Iaii), (Iaiii), and (Iaiv), or pharmaceutically acceptable salts, solvates, hydrates, polymorphs, or combinations thereof whether in crystalline form, **amorphous** form, or a combination thereof, can be used in any such API composition.

SUMM The invention also provides compositions of active pharmaceutical ingredient ("API") comprising any of the above composition embodiments. Advantageously, any of the compositions comprising compounds represented by formulae (Ia) and (Ib) may also comprise any of the specific compositions represented by formulae (Iai)-(Ibi); (Iaii)-(Ibii); (Iaiii)-(Ibiii); and (Iaiv)-(Ibiv) or pharmaceutically acceptable salts, solvates, hydrates, polymorphs, or combinations thereof, whether in crystalline form, **amorphous** form, or a combination thereof,

can be used in any such API compositions.

SUMM Additionally, when using such process represented in the prior art, negligible or trace amounts of previously unknown compounds are formed as described herein. For example, in the preparation of such composition as referenced in the immediately preceding paragraph, compounds having the previously unknown diastereomers S.sub.xa --R.sub.4q and S.sub.xb --R.sub.4z are formed with varying and inconsistent ratios of compounds represented by formulae (Ia) and (Ib). Also formed in trace quantities, and typically in **amorphous** form, are compounds represented by formulae (Ia) and (Ib) having the previously unknown diastereomers S.sub.xa --R.sub.4z and S.sub.xb --R.sub.4q.

SUMM Accordingly, the processes taught in the prior art for the preparation of "omeprazole" as well as "**esomeprazole**" (the intended S-isomer of "omeprazole") provide quantities of previously unknown and unrecognized compounds having pharmaceutical activity, or which are used as intermediates in the preparation of pharmaceutically active compounds of the present invention, or which are used as predrugs which convert to the active metabolite in vivo. Furthermore, many such processes do not invariably provide the same result when conducted as taught in the prior art.

SUMM By employing the above method(s) of obtaining the compound represented by formula (Ia) in solid state, one obtains the (-) and (+) enantiomers as a racemic mixture, with these enantiomers including various amounts of diastereomers as set forth herein. In one embodiment, Applicants have discovered that the (-) and (+) enantiomers may be predominantly present as the S-S and R-R diastereomers respectively. Although not intending to be bound by theory, in this embodiment, the two molecules (i.e., compounds of formulae (Ia) and (Ib)) co-crystallize in a centric space group in which the molecules are related to each other through a center of inversion and linked by hydrogen bonding from the amine hydrogens to the sulfoxide oxygens. The R.sub.4 methoxy methyl is directed towards the center of the bridged complex. Examination of the contact distances in the region where the other methoxy methyl would presumably reside demonstrates that there is not adequate space within the lattice for the other diastereomers (S-S and R-S) to co-exist. In this embodiment, the compound represented by formula (Ia) may comprise about 99 percent (w/w) of the R-R and S-S diastereomers and the remaining percentage of other components which may include, for example, the diastereomers S-R and R-S, generally in **amorphous** form.

SUMM Although not intending to be bound by theory, such compounds of formula (Ia) are believed to be crystalline with little **amorphous** content. However, when grinding is applied to a solid sample comprising the compound of formulae (Ia), and in a preferred embodiment the compounds of formulae (Ia) and (Ib), an increase in the **amorphous** character of the sample is believed to result along with an increase in the amount of compound of formula (Ib). Again, not intending to be bound by theory, it is believed that the sample undergoes a solid state transformation and "recrystallizes" or transforms over a relatively short period of time from the more **amorphous** state to a more crystalline state subsequent to grinding. Nonetheless, it is believed that by performing multiple grinding steps in sequence, (i.e., grinding followed by relaxation followed by grinding) one may obtain a solid sample that becomes more **amorphous** in character and hence comprises a greater amount of the compound of the formula (Ib) as opposed to a sample that has experienced a lower amount of grinding.

SUMM The structure of the compound of formula (Ib) can be confirmed by solid

state techniques such as, for example, X-ray powder diffraction patterns, Raman, FTIR, solid state NMR, and thermal analysis, of the ground material and the unground material. For example, comparison of the two powder patterns showed distinct decreases in intensity, broadening of the peaks, and an increase in the **amorphous** nature for the ground material. The ground material showed a powder pattern that is more consistent with the proposed more **amorphous** nature of the compound of formula (Ib), e.g., 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

DETD The following examples are intended to illustrate the invention, and are not to be construed as limiting the scope of the invention. For the purposes of the examples, the phrase "(5)6-methoxy2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole" refers to a co-crystallized mixture, (with or without an amount of **amorphous** compounds), of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole and 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole, each as determined and referenced herein.

L2 ANSWER 38 OF 42 USPATFULL on STN

ACCESSION NUMBER:	2001:196620 USPATFULL
TITLE:	Method of improving bioavailability
INVENTOR(S):	Whittle, Robert R., 5006 Pine Needles Dr., Wilmington, NC, United States 28403 Sancilio, Frederick D., 2332 Ocean Point Dr., Wilmington, NC, United States 28405 Stowell, Grayson Walker, 710 Darwin Dr., Wilmington, NC, United States 28405 Jenkins, Douglas John, 6400 Purple Martin Ct., Wilmington, NC, United States 28411-8323 Whittall, Linda B., 2204 Splitbrook Ct., Wilmington, NC, United States 28411 Meyer, Glenn Alan, 6117 Clairidge Rd., Wilmington, NC, United States 28403

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6312712	B1	20011106
APPLICATION INFO.:	US 2000-628840		20000731 (9)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 2000-519976, filed on 7 Mar 2000, now patented, Pat. No. US 6262085		

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-150878P	19990826 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	GRANTED
PRIMARY EXAMINER:	Reamer, James H.
LEGAL REPRESENTATIVE:	Myers Bigel Sibley & Sajovec, P.A., Fontana, Esq., Steven A.
NUMBER OF CLAIMS:	12
EXEMPLARY CLAIM:	1
LINE COUNT:	3524

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Improved bioavailability method of one or more of certain pharmaceutically active compounds or pharmaceutically acceptable salts, solvates, hydrates, or combinations thereof that include administering a non-toxic, therapeutically effective amount of the compounds combined with at least one cyclodextrin to a mammal in need of treatment of gastric acid related diseases.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM The teachings regarding the methods of making omeprazole as referred to in these references, salts thereof, enantiomers thereof, and salts of the enantiomers, as well as formulations which may include these compounds, all rely on the chemical structure of omeprazole being accurately determined and the referenced compound or compounds being consistently prepared using the referenced techniques. More specifically, a methoxy group on the benzimidazole ring has been explicitly stated in the literature to be present at the 5-position, in omeprazole, a racemic mixture, and an optically pure isomer of omeprazole designated as **esomeprazole** or **s-omeprazole**. Applicants have now unexpectedly discovered that the complexity of omeprazole and the intricacies of the bioactivity of each of its previously undiscovered attributes has never been disclosed. More specifically, Applicants have confirmed that the methods of the prior art do not yield a single compound having the methoxy group in the 5-position on the benzimidazole ring as previously taught, nor do all of the methods of the prior art yield consistent results. In fact, omeprazole as conventionally referred to as a bulk drug substance (in its solid state) is confirmed to be present in the form of two pharmaceutically active compounds having the methoxy group on the benzimidazole ring at the 6- and 5-positions. Additionally, Applicants have discovered the presence of a second chiral location at the pyridine ring plane in each of the two compounds such that each compound has two positional isomers and four diastereomers. Therefore, the present invention provides these individual compounds, along with any salts, hydrates, solvates, combinations thereof, and polymorphs thereof, compositions of the above, and methods of making the same that are not taught or suggested by the prior art.

SUMM The present invention generally provides compounds represented by formula (Ia), co-crystallized compositions of compounds represented by formulae (Ia) and (Ib) (as well as the potential presence of **amorphous** compound, typically of compounds represented by formula (1b), the presence or amount of which can increase as the percent of such (1b) compounds increases), each described in detail herein, one or more pharmaceutically acceptable salts, solvates, hydrates, or combinations thereof, and complexes thereof. Diastereomers of the above are also provided. The invention also provides compositions and pharmaceutical formulations of the above. Methods of making the above are also provided by the present invention.

SUMM Accordingly, methods of the present invention provide for improved biological activity/efficacy (e.g. inhibition of gastric acid secretions and treatment of gastric acid disturbances in mammals, including humans) of pharmaceutically active compounds omeprazole and **esomeprazole** , as presently known in the art, comprising administering to such mammals in need of treatment a non-toxic, therapeutically effective amount of any composition of the present invention comprising compounds or compositions of the present invention having individual diastereomers comprising S.sub.xa --R.sub.4q ; S.sub.xa --R.sub.4z ; S.sub.xb --R.sub.4q ; or S.sub.xb --R.sub.4z, or pharmaceutically acceptable salts, solvates, hydrates, or combinations thereof. Also provided are such methods wherein said compounds or complexes of the present invention having said selected individual diastereomer pair essentially free of compounds of the present invention having diastereomer pairs other than said selected individual diastereomers. A preferred diastereomer is S.sub.xa --R.sub.4q, and an especially preferred diastereomer is S.sub.xa --R.sub.4z.

SUMM In another aspect, the invention also provides a composition of active pharmaceutical ingredient ("API") comprising any of the above

composition embodiments, each of which may be present in crystalline form. Advantageously, any of the compositions comprising compounds represented by formula (Ia) may also comprise any of the specific compounds represented by formulae (Iai), (Iaii), (Iaiii), and (Iaiv), or pharmaceutically acceptable salts, solvates, hydrates, polymorphs, or combinations thereof whether in crystalline form, **amorphous** form, or a combination thereof, can be used in any such API composition.

SUMM The invention also provides compositions of active pharmaceutical ingredient ("API") comprising any of the above composition embodiments. Advantageously, any of the compositions comprising compounds represented by formulae (Ia) and (Ib) may also comprise any of the specific compositions represented by formulae (Iai)-(Ibi); (Iaii)-(Ibii); (Iaiii)-(Ibiii); and (Iaiv)-(Ibiv) or pharmaceutically acceptable salts, solvates, hydrates, polymorphs, or combinations thereof, whether in crystalline form, **amorphous** form, or a combination thereof, can be used in any such API compositions.

SUMM Additionally, when using such process represented in the prior art, negligible or trace amounts of previously unknown compounds are formed as described herein. For example, in the preparation of such composition as referenced in the immediately preceding paragraph, compounds having the previously unknown diastereomers S.sub.xa --R.sub.4q and S.sub.xb --R.sub.4z are formed with varying and inconsistent ratios of compounds represented by formulae (Ia) and (Ib). Also formed in trace quantities, and typically in **amorphous** form, are compounds represented by formulae (Ia) and (Ib) having the previously unknown diastereomers S.sub.xa --R.sub.4z and S.sub.xb --R.sub.4q.

SUMM Accordingly, the processes taught in the prior art for the preparation of "omeprazole" as well as "**esomeprazole**" (the intended S-isomer of "omeprazole") provide quantities of previously unknown and unrecognized compounds having pharmaceutical activity, or which are used as intermediates in the preparation of pharmaceutically active compounds of the present invention, or which are used as predrugs which convert to the active metabolite in vivo. Furthermore, many such processes do not invariably provide the same result when conducted as taught in the prior art.

SUMM By employing the above method(s) of obtaining the compound represented by formula (Ia) in solid state, one obtains the (-) and (+) enantiomers as a racemic mixture, with these enantiomers including various amounts of diastereomers as set forth herein. In one embodiment, Applicants have discovered that the (-) and (+) enantiomers may be predominantly present as the S--S and R--R diastereomers respectively. Although not intending to be bound by theory, in this embodiment, the two molecules (i.e., compounds of formulae (Ia) and (Ib)) co-crystallize in a centric space group in which the molecules are related to each other through a center of inversion and linked by hydrogen bonding from the amine hydrogens to the sulfoxide oxygens. The R.sub.4 methoxy methyl is directed towards the center of the bridged complex. Examination of the contact distances in the region where the other methoxy methyl would presumably reside demonstrates that there is not adequate space within the lattice for the other diastereomers (S--R and R--S) to co-exist. In this embodiment, the compound represented by formula (Ia) may comprise about 99 percent (w/w) of the R--R and S--S diastereomers and the remaining percentage of other components which may include, for example, the diastereomers S--R and R--S, generally in **amorphous** form.

SUMM Although not intending to be bound by theory, such compounds of formula (Ia) are believed to be crystalline with little **amorphous** content. However, when grinding is applied to a solid sample comprising

the compound of formulae (Ia), and in a preferred embodiment the compounds of formulae (Ia) and (Ib), an increase in the **amorphous** character of the sample is believed to result along with an increase in the amount of compound of formula (Ib). Again, not intending to be bound by theory, it is believed that the sample undergoes a solid state transformation and "recrystallizes" or transforms over a relatively short period of time from the more **amorphous** state to a more crystalline state subsequent to grinding. Nonetheless, it is believed that by performing multiple grinding steps in sequence, (i.e., grinding followed by relaxation followed by grinding) one may obtain a solid sample that becomes more **amorphous** in character and hence comprises a greater amount of the compound of the formula (Ib) as opposed to a sample that has experienced a lower amount of grinding.

SUMM The structure of the compound of formula (Ib) can be confirmed by solid state techniques such as, for example, X-ray powder diffraction patterns, Raman, FTIR, solid state NMR, and thermal analysis, of the ground material and the unground material. For example, comparison of the two powder patterns showed distinct decreases in intensity, broadening of the peaks, and an increase in the **amorphous** nature for the ground material. The ground material showed a powder pattern that is more consistent with the proposed more **amorphous** nature of the compound of formula (Ib), e.g., 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

DETD The following examples are intended to illustrate the invention, and are not to be construed as limiting the scope of the invention. For the purposes of the examples, the phrase "(5)6-methoxy 2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole" refers to a co-crystallized mixture, (with or without an amount of **amorphous** compounds), of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole and 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole, each as determined and referenced herein.

L2 ANSWER 39 OF 42 USPATFULL on STN

ACCESSION NUMBER:	2001:121492 USPATFULL
TITLE:	Dry blend pharmaceutical formulations
INVENTOR(S):	Whittle, Robert R., 5006 Pine Needles Dr., Wilmington, NC, United States 28403 Sancilio, Frederick D., 2332 Ocean Point Dr., Wilmington, NC, United States 28405 Stowell, Grayson Walker, 710 Darwin Dr., Wilmington, NC, United States 28405 Jenkins, Douglas John, 6400 Purple Martin Ct., Wilmington, NC, United States 28411-8323 Whittall, Linda B., 2204 Splitbrook Ct., Wilmington, NC, United States 28411 Fontana, Steven A., 5344 Beretta Way, Wilmington, NC, United States 28409

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6268385	B1	20010731
APPLICATION INFO.:	US 2000-645146		20000824 (9)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 2000-519976, filed on 7 Mar 2000		

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-150878P	19990826 (60)

10/690,897

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Reamer, James H.
LEGAL REPRESENTATIVE: Myers Bigel Sibley & Sajovec, Fontana, Esq., Steven A.
NUMBER OF CLAIMS: 15
EXEMPLARY CLAIM: 1
LINE COUNT: 3880
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides pharmaceutical formulations comprising compositions one or more of certain active pharmaceutical ingredients or pharmaceutically acceptable salts, solvates, hydrates, or combinations thereof wherein the ratio of said one or more active pharmaceutical ingredients in said formulations is essentially the same as the ratio of said active pharmaceutical ingredients in the corresponding, non-formulated drug substance. Methods for using the same are included.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM The teachings regarding the methods of making omeprazole as referred to in these references, salts thereof, enantiomers thereof, and salts of the enantiomers, as well as formulations which may include these compounds, all rely on the chemical structure of omeprazole being accurately determined and the referenced compound or compounds being consistently prepared using the referenced techniques. More specifically, a methoxy group on the benzimidazole ring has been explicitly stated in the literature to be present at the 5-position, in omeprazole, a racemic mixture, and an optically pure isomer of omeprazole designated as **esomeprazole** or **s-omeprazole**. Applicants have now unexpectedly discovered the complexity of omeprazole and the relative bioactivity of each of its previously undiscovered and undisclosed attributes. More specifically, Applicants have confirmed that the methods of the prior art do not yield a single compound having the methoxy group in the 5-position on the benzimidazole ring as previously taught, nor do all of the methods of the prior art yield consistent results. In fact, omeprazole as conventionally referred to as a bulk drug substance (in its solid state) has been discovered to be present in the form of two pharmaceutically active compounds having the methoxy group on the benzimidazole ring at the 6- and 5-positions. Additionally, Applicants have discovered the presence of a second chiral location at the pyridine ring plane in each of the two compounds such that each compound has two positional isomers and four diastereomers. Therefore, the present invention provides these individual compounds, along with any salts, hydrates, solvates, combinations thereof, and polymorphs thereof, compositions of the above, and methods of making the same that are not taught or suggested by the prior art, pharmaceutical formulations of the compounds, compositions, and complexes of the present invention, and methods for using the same.

SUMM Accordingly, methods of the present invention provide for improved biological activity/efficacy (e.g. inhibition of gastric acid secretions and, thus, treatment of gastric acid disturbances in mammals, including humans) of pharmaceutically active compounds omeprazole and **esomeprazole**, as presently known in the art, comprising administering to such mammals in need of treatment a non-toxic, therapeutically effective amount of any composition of the present invention comprising compounds or compositions of the present invention having individual diastereomers comprising S.sub.xa --R.sub.4q ; S.sub.xa --R.sub.4z ; S.sub.xb --R.sub.4q ; or S.sub.xb --R.sub.4z, or one or more pharmaceutically acceptable salts, solvates, hydrates, or combinations thereof. Also provided are such methods wherein said compounds or complexes of the present invention having said selected individual diastereomer pair essentially free of compounds of the present invention having diastereomer pairs other than said selected

individual diastereomers. A preferred diastereomer is S.sub.xa --R.sub.4q, and an especially preferred diastereomer is S.sub.xa --R.sub.4z.

SUMM In another aspect, the invention also provides compositions of active pharmaceutical ingredient ("API") comprising any of the compounds, compositions, or complexes of the present invention, each of which may be present in crystalline form, in part or in whole. Advantageously, each such compositions and/or complexes comprising compounds represented by formula (Ia) may also include any one or more of the specific compounds represented by formulae (Iai), (Iaii), (Iaiii), and (Iaiv), or pharmaceutically acceptable salts, solvates, hydrates, polymorphs, or combinations thereof, whether in crystalline form, **amorphous** form, or a combination thereof. Each can be used as the bases for any such API composition.

SUMM Any of such composition embodiments comprising any of the compounds represented by formulae (Ia) and (Ib), individual species of compounds (Iai)-(Ibi), (Iaii)-(Ibii), (Iaiii)-(Ibiii), and (Iaiv)-(Ibiv), diastereromers thereof, or one or more pharmaceutically acceptable salts, solvates, hydrates, or combinations thereof, may be present in crystalline form, **amorphous** form, or combinations thereof.

SUMM The invention also provides compositions of active pharmaceutical ingredient ("API") comprising any of the above composition embodiments. Advantageously, any of the compositions comprising compounds represented by formulae (Ia) and (Ib) may also comprise any of the specific compositions represented by formulae (Iai)-(Ibi); (Iaii)-(Ibii); (Iaiii)-(Ibiii); and (Iaiv)-(Ibiv) or one or more pharmaceutically acceptable salts, solvates, hydrates, polymorphs, or combinations thereof, whether in crystalline form, **amorphous** form, or a combination thereof, can be used in any such API compositions.

SUMM Additionally, when using such processes represented in the prior art, negligible or trace amounts of previously unknown compounds are formed as described herein. For example, in the preparation of such composition as referenced in the immediately preceding paragraph, compounds having the previously unknown diastereomers S.sub.xa --R.sub.4q and S.sub.xb --R.sub.4z are formed with varying and inconsistent ratios of compounds represented by formulae (Ia) and (Ib). Also formed in trace quantities, and typically in **amorphous** form, are compounds represented by formulae (Ia) and (Ib) having the previously unknown diastereomers S.sub.xa --R.sub.4z and S.sub.xb --R.sub.4q.

SUMM Accordingly, the processes taught in the prior art for the preparation of "omeprazole" as well as "**esomeprazole**" (the intended S-isomer of "omeprazole") provide quantities of previously unknown and unrecognized compounds having pharmaceutical activity, or that are used as intermediates in the preparation of pharmaceutically active compounds of the present invention, or that are used as prodrugs that convert to the active metabolite in vivo. Furthermore, many such processes do not invariably provide the same result when conducted as taught in the prior art.

SUMM By employing the above method(s) of obtaining the compound represented by formula (Ia) in solid state, one obtains the (-) and (+) enantiomers as a racemic mixture, with these enantiomers including various amounts of diastereomers as set forth herein. In one embodiment, Applicants have discovered that the (-) and (+) enantiomers may be predominantly present as the S.sub.xa --R.sub.4q and S.sub.xb --R.sub.4z diastereomers respectively. Although not intending to be bound by theory, in this embodiment, the two molecules (i.e., compounds of formulae (Ia) and

(Ib)) co-crystallize in a centric space group in which the molecules are related to each other through a center of inversion and linked by hydrogen bonding from the amine hydrogens to the sulfoxide oxygens. The R.sub.4 methoxy methyl is directed towards the center of the bridged complex. Examination of the contact distances in the region where the other methoxy methyl would presumably reside demonstrates that there is not adequate space within the lattice for the other diastereomers (S.sub.xa --R.sub.4z and S.sub.xb --R.sub.4q) to co-exist. In this embodiment, the compound represented by formula (Ia) may comprise about 99 percent (w/w) of the S.sub.xb --R.sub.4z and S.sub.xa --R.sub.4q diastereomers and the remaining percentage of other components which may include, for example, the diastereomers S.sub.xa --R.sub.4z and S.sub.xb --R.sub.4q, generally in **amorphous** form.

SUMM Although not intending to be bound by theory, such compounds of formula (Ia) are believed to be crystalline with little **amorphous** content. However, when grinding is applied to a solid sample comprising the compound of formula (Ia), and in a preferred embodiment the compounds of formulae (Ia) and (Ib), an increase in the **amorphous** character of the sample is believed to result along with an increase in the amount of compound of formula (Ib). Again, not intending to be bound by theory, it is believed that the sample undergoes a solid state transformation and "recrystallizes" or transforms over a relatively short period of time from the more **amorphous** state to a more crystalline state subsequent to grinding. Nonetheless, it is believed that by performing multiple grinding steps in sequence, (i.e., grinding followed by relaxation followed by grinding) one may obtain a solid sample that becomes more **amorphous** in character and hence comprises a greater amount of the compound of the formula (Ib) as opposed to a sample that has experienced a lesser amount of grinding.

SUMM The structure of the compound of formula (Ib) can be confirmed by solid state techniques such as, for example, X-ray powder diffraction patterns, Raman, FTIR, solid state NMR, and thermal analysis, of the ground material and the unground material. For example, comparison of the two powder patterns showed distinct decreases in intensity, broadening of the peaks, and an increase in the **amorphous** nature for the ground material. The ground material showed a powder pattern that is more consistent with the proposed more **amorphous** nature of the compound of formula (Ib), e.g., 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

SUMM The following examples are intended to illustrate the invention, and are not to be construed as limiting the scope of the invention. For the purposes of the examples, the phrase "(5)6-methoxy 2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole" refers to a combination of, preferably a co-crystallized mixture, (with or without an amount of **amorphous** compounds), of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole and 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole, each as determined and referenced herein.

L2 ANSWER 40 OF 42 USPATFULL on STN
ACCESSION NUMBER: 2001:112351 USPATFULL
TITLE: Pharmaceutical unit dosage form
INVENTOR(S): Whittle, Robert R., 5006 Pine Needles Dr., Wilmington, NC, United States 28403
Sancilio, Frederick D., 2332 Ocean Point Dr., Wilmington, NC, United States 28405
Stowell, Grayson Walker, 710 Darwin Dr., Wilmington,

NC, United States 28405
Jenkins, Douglas John, 6400 Purple Martin Ct., Wilmington, NC, United States 28411-8323
Whittall, Linda B., 2204 Splitbrook Ct., Wilmington, NC, United States 28411
Fontana, Steven A., 5344 Beretta Way, Wilmington, NC, United States 28409

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6262086	B1	20010717
APPLICATION INFO.:	US 2000-630022		20000731 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2000-519976, filed on 7 Mar 2000

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-150878P	19990826 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Reamer, James H.
LEGAL REPRESENTATIVE: Myers Bigel Sibley & Sajovec, Fontana, Esq., Steven A.
NUMBER OF CLAIMS: 16
EXEMPLARY CLAIM: 1
LINE COUNT: 3527

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Pharmaceutical oral unit dosage forms are comprised of, per dosage unit, one or more active ingredients or pharmaceutically acceptable salts, solvates, hydrates, or combinations thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM The teachings regarding the methods of making omeprazole as referred to in these references, salts thereof, enantiomers thereof, and salts of the enantiomers, as well as formulations which may include these compounds, all rely on the chemical structure of omeprazole being accurately determined and the referenced compound or compounds being consistently prepared using the referenced techniques. More specifically, a methoxy group on the benzimidazole ring has been explicitly stated in the literature to be present at the 5-position, in omeprazole, a racemic mixture, and an optically pure isomer of omeprazole designated as **esomeprazole** or **s-omeprazole**. Applicants have now unexpectedly discovered that the complexity of omeprazole and the intricacies of the bioactivity of each of its previously undiscovered attributes has never been disclosed. More specifically, Applicants have confirmed that the methods of the prior art do not yield a single compound having the methoxy group in the 5-position on the benzimidazole ring as previously taught, nor do all of the methods of the prior art yield consistent results. In fact, omeprazole as conventionally referred to as a bulk drug substance (in its solid state) is confirmed to be present in the form of two pharmaceutically active compounds having the methoxy group on the benzimidazole ring at the 6- and 5-positions. Additionally, Applicants have discovered the presence of a second chiral location at the pyridine ring plane in each of the two compounds such that each compound has two positional isomers and four diastereomers. Therefore, the present invention provides these individual compounds, along with any salts, hydrates, solvates, combinations thereof, and polymorphs thereof, compositions of the above, and methods of making the same that are not taught or suggested by the prior art.

SUMM The present invention generally provides compounds represented by formula (Ia), co-crystallized compositions of compounds represented by

formulae (Ia) and (Ib) (as well as the potential presence of **amorphous** compound, typically of compounds represented by formula (Ib), the presence or amount of which can increase as the percent of such (Ib) compounds increases), each described in detail herein, one or more pharmaceutically acceptable salts, solvates, hydrates, or combinations thereof, and complexes thereof. Diastereomers of the above are also provided. The invention also provides compositions and pharmaceutical formulations of the above. Methods of making the above are also provided by the present invention.

SUMM Accordingly, methods of the present invention provide for improved biological activity/efficacy (e.g. inhibition of gastric acid secretions and treatment of gastric acid disturbances in mammals, including humans) of pharmaceutically active compounds omeprazole and **esomeprazole** , as presently known in the art, comprising administering to such mammals in need of treatment a non-toxic, therapeutically effective amount of any composition of the present invention comprising compounds or compositions of the present invention having individual diastereomers comprising S.sub.xa -R.sub.4q, S.sub.xa -R.sub.4z ; S.sub.xb -R.sub.4q ; or S.sub.xb -R.sub.4z, or pharmaceutically acceptable salts, solvates, hydrates, or combinations thereof. Also provided are such methods wherein said compounds or complexes of the present invention having said selected individual diastereomer pair essentially free of compounds of the present invention having diastereomer pairs other than said selected individual diastereomers. A preferred diastereomer is S.sub.xa -R.sub.4q, and an especially preferred diastereomer is S.sub.xa -R.sub.4z.

SUMM In another aspect, the invention also provides a composition of active pharmaceutical ingredient ("API") comprising any of the above composition embodiments, each of which may be present in crystalline form. Advantageously, any of the compositions comprising compounds represented by formula (Ia) may also comprise any of the specific compounds represented by formulae (Iai), (Iaii), (Iaiii), and (Iaiv), or pharmaceutically acceptable salts, solvates, hydrates, polymorphs, or combinations thereof whether in crystalline form, **amorphous** form, or a combination thereof, can be used in any such API composition.

SUMM The invention also provides compositions of active pharmaceutical ingredient ("API") comprising any of the above composition embodiments. Advantageously, any of the compositions comprising compounds represented by formulae (Ia) and (Ib) may also comprise any of the specific compositions represented by formulae (Iai)-(Ibi); (Iaii)-(Ibii); (Iaiii)-(Ibiii); and (Iaiv)-(Ibiv) or pharmaceutically acceptable salts, solvates, hydrates, polymorphs, or combinations thereof, whether in crystalline form, **amorphous** form, or a combination thereof, can be used in any such API compositions.

SUMM Additionally, when using such process represented in the prior art, negligible or trace amounts of previously unknown compounds are formed as described herein. For example, in the preparation of such composition as referenced in the immediately preceding paragraph, compounds having the previously unknown diastereomers S.sub.xa -R.sub.4q and S.sub.xb -R.sub.4z are formed with varying and inconsistent ratios of compounds represented by formulae (Ia) and (Ib). Also formed in trace quantities, and typically in **amorphous** form, are compounds represented by formulae (Ia) and (Ib) having the previously unknown diastereomers S.sub.xa -R.sub.4z and S.sub.xb -R.sub.4q.

SUMM Accordingly, the processes taught in the prior art for the preparation of "omeprazole" as well as "**esomeprazole**" (the intended S-isomer of "omeprazole") provide quantities of previously unknown and

unrecognized compounds having pharmaceutical activity, or which are used as intermediates in the preparation of pharmaceutically active compounds of the present invention, or which are used as predrugs which convert to the active metabolite in vivo. Furthermore, many such processes do not invariably provide the same result when conducted as taught in the prior art.

SUMM By employing the above method(s) of obtaining the compound represented by formula (Ia) in solid state, one obtains the (-) and (+) enantiomers as a racemic mixture, with these enantiomers including various amounts of diastereomers as set forth herein. In one embodiment, Applicants have discovered that the (-) and (+) enantiomers may be predominantly present as the S-S and R-R diastereomers respectively. Although not intending to be bound by theory, in this embodiment, the two molecules (i.e., compounds of formulae (Ia) and (Ib)) co-crystallize in a centric space group in which the molecules are related to each other through a center of inversion and linked by hydrogen bonding from the amine hydrogens to the sulfoxide oxygens. The R.sub.4 methoxy methyl is directed towards the center of the bridged complex. Examination of the contact distances in the region where the other methoxy methyl would presumably reside demonstrates that there is not adequate space within the lattice for the other diastereomers (S-R and R-S) to co-exist. In this embodiment, the compound represented by formula (Ia) may comprise about 99 percent (w/w) of the R-R and S-S diastereomers and the remaining percentage of other components which may include, for example, the diastereomers S-R and R-S, generally in **amorphous** form.

SUMM Although not intending to be bound by theory, such compounds of formula (Ia) are believed to be crystalline with little **amorphous** content. However, when grinding is applied to a solid sample comprising the compound of formulae (Ia), and in a preferred embodiment the compounds of formulae (Ia) and (Ib), an increase in the **amorphous** character of the sample is believed to result along with an increase in the amount of compound of formula (Ib). Again, not intending to be bound by theory, it is believed that the sample undergoes a solid state transformation and "recrystallizes" or transforms over a relatively short period of time from the more **amorphous** state to a more crystalline state subsequent to grinding. Nonetheless, it is believed that by performing multiple grinding steps in sequence, (i.e., grinding followed by relaxation followed by grinding) one may obtain a solid sample that becomes more **amorphous** in character and hence comprises a greater amount of the compound of the formula (Ib) as opposed to a sample that has experienced a lower amount of grinding.

SUMM The structure of the compound of formula (Ib) can be confirmed by solid state techniques such as, for example, X-ray powder diffraction patterns, Raman, FTIR, solid state NMR, and thermal analysis, of the ground material and the unground material. For example, comparison of the two powder patterns showed distinct decreases in intensity, broadening of the peaks, and an increase in the **amorphous** nature for the ground material. The ground material showed a powder pattern that is more consistent with the proposed more **amorphous** nature of the compound of formula (Ib), e.g., 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

SUMM The following examples are intended to illustrate the invention, and are not to be construed as limiting the scope of the invention. For the purposes of the examples, the phrase "(5)6-methoxy 2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole" refers to a co-crystallized mixture, (with or without an amount of **amorphous** compounds), of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-

methyl]sulfinyl]-1H-benzimidazole and 6-methoxy-2-[[(4-methoxy-3, 5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole, each as determined and referenced herein.

L2 ANSWER 41 OF 42 USPATFULL on STN
ACCESSION NUMBER: 2001:112350 USPATFULL
TITLE: Alkoxy substituted Benzimidazole compounds, pharmaceutical preparations containing the same, and methods of using the same
INVENTOR(S): Whittle, Robert R., 5006 Pine Needles Dr., Wilmington, NC, United States 28403
Sancilio, Frederick D., 2332 Ocean Point Dr., Wilmington, NC, United States 28405
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	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6262085	B1	20010717	
APPLICATION INFO.:	US 2000-519976		20000307	(9)

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PRIORITY INFORMATION:	US 1999-150878P	19990826	(60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Reamer, James H.
LEGAL REPRESENTATIVE: Myers Bigel Sibley & Sajovec, P.A., Fontana, Esq., Steven A.
NUMBER OF CLAIMS: 12
EXEMPLARY CLAIM: 1,2,3
LINE COUNT: 2583
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Compounds of the formula (Ia) are disclosed by the invention, along with compositions thereof optionally in combination with compounds of formulae (Ib). Methods of making and using the same are also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM The teachings regarding the methods of making omeprazole as referred to in these references, salts thereof, enantiomers thereof, and salts of the enantiomers, as well as formulations which may include these compounds, all rely on the chemical structure of omeprazole being accurately determined and the referenced compound or compounds being consistently prepared using the referenced techniques. More specifically, a methoxy group on the benzimidazole ring has been explicitly stated in the literature to be present at the 5-position, in omeprazole, a racemic mixture, and an optically pure isomer of omeprazole designated as **esomeprazole** or **s-omeprazole**. Applicants have now unexpectedly discovered that the complexity of omeprazole and the intricacies of the bioactivity of each of its previously undiscovered attributes has never been disclosed. More specifically, Applicants have confirmed that the methods of the prior art do not yield a single compound having the methoxy group in the 5-position on the benzimidazole ring as previously taught, nor do all of the methods of the prior art yield consistent results. In fact, omeprazole as conventionally referred to as a bulk drug substance (in its solid state) is confirmed to be present in the form of two

pharmaceutically active compounds having the methoxy group on the benzimidazole ring at the 6- and 5-positions. Additionally, Applicants have discovered the presence of a second chiral location at the pyridine ring plane in each of the two compounds such that each compound has two positional isomers and four diastereomers. Therefore, the present invention provides these individual compounds, along with any salts, hydrates, solvates, combinations thereof, and polymorphs thereof, compositions of the above, and methods of making the same which are not taught or suggested by the prior art.

SUMM Accordingly, methods of the present invention provide for improved biological activity/efficacy (e.g. inhibition of gastric acid secretions and treatment of gastric acid disturbances in mammals, including humans) of pharmaceutically active compounds omeprazole and **esomeprazole** , as presently known in the art, comprising administering to such mammals in need of treatment any composition of the present invention comprising compounds or compositions of the present invention having an individual diastereomers comprising S.sub.xa --R.sub.4q ; S.sub.xa --R.sub.4z ; S.sub.xb --R.sub.4q ; or S.sub.xb --R.sub.4z, or one or more pharmaceutically acceptable salts, solvates, hydrates, or combinations thereof. Also provided are such methods wherein said compounds or complexes of the present invention having said selected individual diastereomer pair essentially free of compounds of the present invention having diastereomer pairs other than said selected individual diastereomers. A preferred diastereomer is S.sub.xa --R.sub.4q, and an especially preferred diastereomer is S.sub.xa --R.sub.4z.

SUMM In another aspect, the invention also provides a composition of active pharmaceutical ingredient ("API") comprising any of the above composition embodiments, each of which may be present in crystalline form. Advantageously, any of the compositions comprising compounds represented by formula (Ia) may also comprise any of the specific compounds represented by formulae (Iai), (Iaii), (Iaiii), and (Iaiv), or one or more pharmaceutically acceptable salts, solvates, hydrates, polymorphs, or combinations thereof whether in crystalline form, **amorphous** form, or a combination thereof, can be used in any such API composition.

SUMM The invention also provides compositions of active pharmaceutical ingredient ("API") comprising any of the above composition embodiments. Advantageously, any of the compositions comprising compounds represented by formulae (Ia) and (Ib) may also comprise any of the specific compositions represented by formulae (Iai)-(Ibi); (Iaii)-(Ibii); (Iaiii)-(Ibiii); and (Iaiv)-(Ibiv) or one or more pharmaceutically acceptable salts, solvates, hydrates, polymorphs, or combinations thereof, whether in crystalline form, **amorphous** form, or a combination thereof, can be used in any such API compositions.

SUMM Additionally, when using such process represented in the prior art, negligible or trace amounts of previously unknown compounds are formed as described herein. For example, in the preparation of "omeprazole" as referenced in the immediately preceding paragraph, compounds having the previously unknown diastereomers S.sub.xa --R.sub.4q and S.sub.xb --R.sub.4z are formed with varying and inconsistent ratios of compounds represented by formulae (Ia) and (Ib). Also formed in trace quantities, and typically in **amorphous** form, are compounds represented by formulae (Ia) and (Ib) having the previously unknown diastereomers S.sub.xa --R.sub.4z and S.sub.xb --R.sub.4q.

SUMM Accordingly, the processes taught in the prior art for the preparation of "omeprazole" as well as "**esomeprazole**" (the intended

S-isomer of "omeprazole") provide quantities of previously unknown and unrecognized compounds having pharmaceutical activity, or which are used as intermediates in the preparation of pharmaceutically active compounds of the present invention. Furthermore, many such processes do not invariably provide the same result when conducted as taught in the prior art.

SUMM By employing the above method of obtaining the compound represented by formula (Ia) in solid state, one obtains the (-) and (+) enantiomers as a racemic mixture, with these enantiomers including various amounts of diastereomers as set forth herein. In one embodiment, Applicants have discovered that the (-) and (+) enantiomers may be predominantly present as the S--S and R--R diastereomers respectively. Although not intending to be bound by theory, in this embodiment, the two molecules (i.e., compounds of formulae (Ia) and (Ib)) co-crystallize in a centric space group in which the molecules are related to each other through a center of inversion and linked by hydrogen bonding from the amine hydrogens to the sulfoxide oxygens. The methoxy methyl is directed towards the center of the bridged complex. Examination of the contact distances in the region where the other methoxy methyl would presumably reside demonstrates that there is not adequate space within the lattice for the other diastereomers (S--R and R--S) to co-exist. In this embodiment, the compound represented by formula (Ia) may comprise about 99 percent (w/w) of the R--R and S--S diastereomers and the remaining percentage of other components which may include, for example, the diastereomers S--R and R--S, generally in **amorphous** form.

SUMM Although not intending to be bound by theory, the compound of formula (Ia) is believed to be crystalline with little **amorphous** content. However, when grinding is applied to a solid sample comprising the compound of formulas (Ia), and in a preferred embodiment the compounds of formulae (Ia) and (Ib), an increase in the **amorphous** character of the sample is believed to result along with an increase in the amount of compound of formula (Ib). Again not intending to be bound by theory, it is believed that the sample undergoes a solid state transformation and "recrystallizes" or transforms over a relatively short period of time from the more **amorphous** state to a more crystalline state subsequent to grinding. Nonetheless, it is believed that by performing multiple grinding steps in sequence, (i.e., grinding followed by relaxation followed by grinding) one may obtain a solid sample that becomes more **amorphous** in character and hence comprises a greater amount of the compound of the formula (Ib) as opposed to a sample that has experienced a lower amount of grinding.

SUMM The structure of the compound of formula (Ib) can be confirmed by solid state techniques such as, for example, X-ray powder diffraction patterns, Raman, FTIR, solid state NMR, and thermal analysis, of the ground material and the unground material. For example, comparison of the two powder patterns showed distinct decreases in intensity, broadening of the peaks, and an increase in the **amorphous** nature for the ground material. The ground material showed a powder pattern that is more consistent with the proposed more **amorphous** nature of the compound of formula (Ib), e.g., 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

L2 ANSWER 42 OF 42 USPATFULL on STN
ACCESSION NUMBER: 2000:171040 USPATFULL
TITLE: Crystalline form of the S-enantiomer of omeprazole
INVENTOR(S): Bohlin, Martin, Johanneshov, Sweden
Horvath, Karol, Sodertalje, Sweden

10/690,897

PATENT ASSIGNEE(S): AstraZeneca AB, Sodertalje, Sweden (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6162816		20001219	
	WO 9828294		19980702	
APPLICATION INFO.:	US 1998-154		19980128	(9)
	WO 1997-SE2125		19971216	
			19990128	PCT 371 date
			19990128	PCT 102(e) date

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PRIORITY INFORMATION:	SE 1996-4793	19961220

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Rotman, Alan L.
LEGAL REPRESENTATIVE: White & Case LLP
NUMBER OF CLAIMS: 17
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Figure(s); 2 Drawing Page(s)
LINE COUNT: 457
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention provides **S-omeprazole** in a neutral form characterised in that it is in a solid state, preferably in a partly crystalline or substantially crystalline state, such as form A or form B. Furthermore, the invention provides processes for the preparation of **S-omeprazole** and its use in medicine.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention provides **S-omeprazole** in a neutral form characterised in that it is in a solid state, preferably in a partly crystalline or substantially crystalline state, such as form A or form B. Furthermore, the invention provides processes for the preparation of **S-omeprazole** and its use in medicine.

SUMM Omeprazole is a sulfoxide and a chiral compound, wherein the sulfur atom being the stereogenic center. Thus, omeprazole is a racemic mixture of its two single enantiomers, the R-omeprazole and the **S-omeprazole**. The absolute configurations of the enantiomers of omeprazole have been determined by an X-ray study of an N akylated derivative of the (+)-enantiomer in neutral form. The (+)-enantiomer of the neutral form and the (-)-enantiomer of the neutral form were found to have the R and S configuration, respectively. The conditions for the optical rotation measurement for each of these enantiomers are described in WO 94/27988.

SUMM WO 92/08716 discloses R-omeprazole in its neutral form as an **amorphous** solid in Example 6. Different salts of the single enantiomers of omeprazole are described in WO 94/27988. The latter document discloses the preparation of the neutral form of the S-enantiomer of omeprazole in, for example, Example 10. However, it was obtained in the form of a syrup or oil which is unsuitable for pharmaceutical use because of the difficulty of handling an oil and incorporating it into solid pharmaceutical compositions, especially in a reproducible manner.

SUMM According to the invention there is provided **S-omeprazole** in a neutral form, i.e. not in the form of a salt, characterised in that the **S-omeprazole** is in a solid state.

SUMM Neutral **S-omeprazole** according to the invention is advantageous because it is more stable, easier to handle and store. It is also easier to characterise because it exists in a more well defined state, easier to purify and easier to synthesise in a reproducible manner.

SUMM **S-Omeprazole** according to the invention can in general be in an **amorphous**, partly crystalline or substantially crystalline solid state. Preferably it is in a partly crystalline solid state or a substantially crystalline solid state. More preferably it is in either of form A which is a crystalline form or form B which is a less crystalline form.

DRWD FIG. 1 shows the X-ray powder diffraction pattern of neutral **S-omeprazole** in form A.

DRWD FIG. 2 shows the X-ray powder diffraction pattern of neutral **S-omeprazole** in form B.

DETD Forms A and B of **S-omeprazole** in neutral form are characterised by having X-ray powder diffraction patterns having the 20 degree angles, d-values and relative intensities given in Table 1.

DETD More particularly, neutral **S-omeprazole** in form A is characterised by the X-ray powder diffraction pattern given in FIG. 1 and neutral **S-omeprazole** in form B is characterised by the X-ray powder diffraction pattern given in FIG. 2. The X-ray powder diffraction (XRD) patterns in these were obtained in Bragg-Bretano geometry. Since form B is less crystalline and also has peaks in its powder diffractogram which are related to peaks in the diffractogram of form A it is not clear that this is a different crystal form.

DETD The expression **S-omeprazole** refers to the fact that it is substantially free of the R-enantiomer, preferably with an enantiomeric excess of 90%, and more preferably 95% e.e.

DETD In a further aspect, the invention relates to processes for the preparation of neutral **S-omeprazole** in a solid state which comprise

DETD (a) evaporating a solution of neutral **S-omeprazole** in one or more organic solvents to a highly concentrated solution, adding a further solvent to the highly concentrated solution and evaporating further until solid **amorphous** neutral **S-omeprazole** is formed; or

DETD (b) crystallization from a solution of **S-omeprazole** in one or more organic solvents and optionally water; or

DETD (c) precipitation from a solution of an alkaline salt of **S-omeprazole** in water and, optionally one or more organic solvents, with a suitable acid.

DETD Process (a) might be further defined by the following aspects. The highly concentrated solution formed in process (a) should not be so concentrated that it is not possible to carry out the second half of the process. After the further evaporation, additional amounts of a further solvent, i.e. a second solvent, may optionally be added and the remaining solvent is evaporated until no more solvent can be removed. This further solvent is preferably one in which neutral **S-omeprazole** is soluble, but not very soluble, and is more preferably an anti-solvent. The repeated evaporation procedure helps to remove all the initial solvent which otherwise would prevent the formation of a solid substance. The resulting **amorphous** precipitate may optionally be further dried, for instance under reduced pressure.

DETD More particularly process (a) may be carried out by dissolving a water soluble salt of **S-omeprazole**, preferably by using an alkali metal salt (e.g. the potassium or preferably sodium salt) in water and extracting neutral **S-omeprazole** to a water

immiscible solvent or water immiscible solvent mixture (e.g. methylene chloride or toluene, preferably methylene chloride), by decreasing the pH in the water phase, e.g. from about 11, preferably to a pH of from 7 to 10 (e.g. to a pH of from 7 to 8) with a water soluble acid (e.g. aqueous HCl or aqueous acetic acid, preferably diluted acetic acid). The organic phase containing the neutral form of **S-omeprazole** may be separated from the water phase and solvent evaporated until a highly concentrated solution is formed, preferably leaving 1-2 ml solvent/g of **S-omeprazole**. A first portion of a further solvent, e.g iso-octane or n-heptane, is added in an amount of, for example, 5-10 m/g of **S-omeprazole**. More solvent is evaporated from the resulting mixture until solid **amorphous** neutral **S-omeprazole** is formed. Further amounts of a further solvent, e.g. 5-10 ml/g of **S-omeprazole**, may be added and re-evaporated until no more solvent can be removed. The resulting solid **amorphous** neutral **S-omeprazole** may optionally be further dried, for instance under reduced pressure.

DETD Process (b) might be further defined by the following aspects. The solution of neutral **S-omeprazole** used in the process (b) of the invention can be formed either (i) by dissolution of already isolated neutral **S-omeprazole**, for instance from process (a) or (ii) it can be the result of a previous step where neutral **S-omeprazole** is formed by chemical reaction, or (iii) it can be a solution formed by extraction.

DETD Crystallization in process (b) may be induced by decreasing the solubility of **S-omeprazole**, e.g. by cooling the mixture, by evaporation of some of the solvents or by mixing with, e.g. by adding, some precipitating solvent or anti-solvent. The crystallization may start spontaneously, but it is preferable to add seeds of the desired form of neutral **S-omeprazole**. Most preferably seeds of **S-omeprazole** form A are added.

DETD Suitable solvents, in which neutral **S-omeprazole** is soluble but not very soluble and which are preferably used for preparing solutions for use in process (b) by dissolution of neutral **S-omeprazole**, are, for example, ethyl acetate, iso-butanol, isopropanol, methyl isobutyl ketone, acetone, and acetonitrile. Preferably the solvent is ethyl acetate or acetonitrile; most preferably it is ethyl acetate. The preferred amount of organic solvent is 4-10 ml/g of **S-omeprazole**.

DETD Suitable organic solvents in which neutral **S-omeprazole** is very soluble which are suitable for use when the solution in process (b) is a reaction solution or obtained by extraction, are, for example, methylene chloride and toluene. Since neutral **S-omeprazole** is very soluble in these solvents, it can be necessary to use an anti-solvent to induce crystallisation.

DETD Process (c) might be further defined as described below. Process (c) according to the invention is preferably carried out by dissolving a water soluble salt of **S-omeprazole** in water or a mixture of water and an organic solvent and crystallisation is induced by mixing with, e.g by addition of, a solution of an acid such that the pH of the final solution is still high enough to prevent significant degradation of the product. The organic solvent(s) is preferably a water miscible solvent(s) such as for instance, acetone, acetonitrile or a lower alkyl alcohol. The acid may be, for example, HCl or acetic acid, preferably aqueous acetic acid. The pH of the final solution may be, for example, from 7 to 10, preferably from 7 to 8.

DETD The starting material of process (c) of the invention is preferably a water soluble salt of **S-omeprazole**, for example an alkali metal salt, particularly a sodium salt. The resulting precipitate

of neutral **S-omeprazole** is generally in a partly crystalline solid state, in particular, in form B.

DETD When the neutral **S-omeprazole** is crystallized, as in processes (b) and (c), the crystals may be separated from the solution, e.g. by filtration or centrifugation, followed by washing with a washing liquid, preferably a solvent mixture in which the particular form of neutral **S-omeprazole** has a very low solubility, for example, an anti-solvent. The preferred proportion of washing liquid to product is from 1:1 to 5:1 by weight. The separated neutral **S-omeprazole** crystals are preferably dried under conditions which avoid degradation of the product, e.g at +30 to +40° C., preferably at reduced pressure of e.g. 10 to 20 mbar, for e.g. 10 to 48 hours.

DETD Neutral **S-omeprazole** according to the invention is effective as a gastric acid secretion inhibitor, and is useful as an antiulcer agent. In a more general sense, it can be used for prevention and treatment of gastric-acid related conditions in mammals and especially in man, including e.g. reflux esophagitis, gastritis, duodenitis, gastric ulcer and duodenal ulcer. Furthermore, it may be used for treatment of other gastrointestinal disorders where gastric acid inhibitory effect is desirable e.g. in patients on NSAID therapy, in patients with Non Ulcer Dyspepsia, in patients with symptomatic gastro-esophageal reflux disease, and in patients with gastrinomas. Neutral **S-omeprazole** according to the invention may also be used in patients in intensive care situations, in patients with acute upper gastrointestinal bleeding, pre- and postoperatively to prevent aspiration of gastric acid and to prevent and treat stress ulceration. Further, neutral **S-omeprazole** may be useful in the treatment of psoriasis as well as in the treatment of Helicobacter infections and diseases related to these.

DETD Any suitable route of administration may be employed for providing the patient with an effective dosage of neutral **S-omeprazole** according to the invention. For example, peroral or parental formulations and the like may be employed. Dosage forms include capsules, tablets, dispersions, suspensions and the like.

DETD According to the invention there is further provided a pharmaceutical composition comprising neutral **S-omeprazole** according to the invention, as active ingredient, in association with a pharmaceutically acceptable carrier, diluent or excipient and optionally other therapeutic ingredients. Compositions comprising other therapeutic ingredients are especially of interest in the treatment of Helicobacter infections. The invention also provides the use of neutral **S-omeprazole** according to the invention in the manufacture of a medicament for use in the treatment of a gastric-acid related condition and a method of treating a gastric-acid related condition which method comprises administering to a subject suffering from a said condition a therapeutically effective amount of neutral **S-omeprazole** according to the invention.

DETD The most suitable route of administration as well as the magnitude of a therapeutic dose of neutral **S-omeprazole** according to the invention in any given case will depend on the nature and severity of the disease to be treated. The dose, and dose frequency, may also vary according to the age, body weight, and response of the individual patient. Special requirements may be needed for patients having Zollinger-Ellison syndrom, such as a need for higher doses than the average patient. Children and patients with liver diseases generally will benefit from doses that are somewhat lower than the average. Thus, in some conditions it may be necessary to use doses outside the ranges stated below. Such higher and lower doses are within the scope of the present invention.

DETD Neutral **S-omeprazole** according to the invention may be combined as the active component in intimate admixture with a

pharmaceutical carrier according to conventional techniques, such as the oral formulations described in WO 96/ 01623 and EP 247 983, the disclosures of which are hereby incorporated as a whole by reference.

DETD The invention is illustrated by the following examples which should not be interpreted as limiting the invention. The best mode to carry out the invention is according to one of the examples giving **S-omeprazole** form A.

DETD Sodium salt of **S-omeprazole** (8 g) was dissolved in water (80 ml) at room temperature. Methylene chloride (80 ml) was added and the product was extracted to the organic phase by addition of diluted (4.8 ml, 25% v/v) acetic acid. The mixture was stirred for 5 minutes and then the two phases were allowed to separate. The organic phase was separated off and charged into a round flask. The methylene chloride was evaporated under vacuum until a highly concentrated solution containing approximately 1 ml of methylene chloride per 1 g of omeprazole was formed. Iso-octane (40 ml) was added and the solvent was evaporated again until an almost dry, **amorphous** substance was formed. A further amount of iso-octane was added (20 ml) and the slurry was concentrated by evaporation. The solid material was dried in an oven at 30° C. under reduced pressure overnight to give 6.5 g solid **amorphous** neutral **S-omeprazole.**

DETD Examples 2 to 7 inclusive illustrate the preparation of neutral **S-omeprazole** form A by recrystallization of the **amorphous** substance prepared in Example 1.

DETD **Amorphous** neutral **S-omeprazole** (0.5 g) was dissolved in ethyl acetate (2g). The solution was placed over night in the refrigerator (-20° C.). Crystals were formed spontaneously. The slurry of crystals obtained was used for seeding in some of the following Examples.

DETD **Amorphous** neutral **S-omeprazole** (2 g) was dissolved in ethyl acetate (20 ml) at room temperature. The solution was seeded with the crystals obtained in Example 2 and allowed to crystallize overnight. The crystals obtained were washed with ethyl acetate (2+2 ml) and dried at +20 C. in air to give 1.3 g of neutral **S-omeprazole** form A.

DETD **Amorphous** neutral **S-omeprazole** (0.5 g) was dissolved in 2 ml methylene chloride and 4 ml iso-octane was added. The solution was seeded with a small amount of neutral **S-omeprazole** form A. After 4 days crystals were formed. The substance was filtered off and washed with iso-octane (1 ml) and dried at room temperature.

DETD **Amorphous** neutral **S-omeprazole** (5.0 g) was dissolved at room temperature in ethyl acetate (40 ml) and a small amount of water (0.5 ml) was added. The solution was seeded with crystalline neutral **S-omeprazole** form A and cooled to 0° C. The solution was allowed to crystallize overnight at 0° C. The resulting crystals were filtered off, washed with ethyl acetate (3+5 ml) and dried at +40° C. under reduced pressure to give 3.4 g neutral **S-omeprazole** form A.

DETD **Amorphous** neutral **S-omeprazole** (3 g) was dissolved in toluene (9 ml) at room temperature and ethyl acetate (20 ml) was added. The solution was seeded with neutral **S-omeprazole** form A and was allowed to crystallize at room temperature for about half an hour. Further ethyl acetate was added (9 ml) and the solution was allowed to crystallise overnight. Then the slurry was cooled to 0° C. and allowed to crystallise for 20 hours. The crystals were filtered off, washed with iso-octane (2+5 ml) and dried at +40° C. under reduced pressure giving 2.0 g of neutral **S-omeprazole** form A.

DETD Preparation of neutral **S-omeprazole** form A from an extraction solution in methylene chloride.

DETD Sodium salt of **S-omeprazole** (20 g) was dissolved in

water (200 ml) at room temperature. Methylene chloride (200 ml) was added. The two phase mixture was agitated and aqueous acetic acid (25% v/v, 12.5 ml) was added. The mixture was stirred for 15 minutes and then the phases were allowed to separate. The methylene chloride solution was charged into a round flask and solvent was evaporated until the dilution was 4 ml methylene chloride per gram of **S-omeprazole** . 18.9 g of this solution, containing 3 g of **S-omeprazole**, was added to a round flask. Acetontrile was added (50 ml) and the solution was seeded with neutral **S-omeprazole** form A and left overnight. The methylene chloride was evaporated until 22.5 ml solvent remained. The solution was then allowed to crystallize overnight at room temperature. 15 ml of ethyl acetate was added and the resulting mixture filtered. The crystals were washed with ethyl acetate (3+3 ml) and dried at +40° C. under reduced pressure to give 1.0 g neutral **S-omeprazole** form A.

DETD Preparation of neutral **S-omeprazole** form A by crystallization from a solution of **S-omeprazole.**

DETD A reaction mixture containing **S-omeprazole** (1.9 g) in toluene is concentrated by evaporation of toluen until the concentration is 0.71 g/ml toluene. Then ethyl acetate (16 ml) is added to the solution. At room temperature the solution is seeded with 0.2 g neutral **S-omeprazole** form A and cooled to 0° C. The solution was allowed to crystallize overnight at 0° C. The resulting crystals were filtered off, washed with ethyl acetate (2+4 ml) and dried at 30° C. under reduced pressure to give 0.89 g neutral **S-omeprazole**, form A.

DETD Preparation of neutral **S-omeprazole** form A by re-crystallization.

DETD Partly crystalline **S-omeprazole**, form A (5.0 g) was dissolved in 258 ml ethyl acetate at 40° C. The solution was cooled to room temperature and the ethyl acetate was slowly evaporated under reduced pressure until 43 ml ethyl acetate remained. At room temperature, the concentrated solution was seeded with neutral **S-omeprazole** form A. The slurry was then cooled to 0° C. for 5 hours. Then, ethyl acetate (6.7 ml) was added and the resulting slurry filtered. The crystals were re-slurried in 20 ml ethyl acetate, the solvent was filtered off and the crystals dried at 25° C. under reduced pressure to give 2.9 g neutral **S-omeprazole** form A.

DETD Preparation of neutral **S-omeprazole** form B by reaction crystallization from a water/acetone (80/20 % v/v) mixture. The sodium salt of **S-omeprazole** (2 g) was dissolved in a mixture of water (16 ml) and acetone (4 ml). Aqueous acetic acid (25 % v/v) was slowly added to the solution in an amount of 0.45 ml which was until the solution had a pH of 10. The resulting slurry was left overnight at room temperature and the cystals were filtered off and washed with water (3+5 ml), dried at +40° C. under reduced pressure giving 0.9 g neutral **S-omeprazole** form B.

DETD Preparation of neutral **S-omeprazole** form B by reaction crystallization from a water/acetone (90/10% v/v) mixture.

DETD The sodium salt of **S-omeprazole** (5.2 g) was dissolved in water (46.9 ml). Acetone (5.2 ml) was added to the solution. Under vigorous stirring, 3.2 ml of aqueous acetic acid (25% v/v) was slowly added. Crystallization started when the pH reached 10. At the end of the addition the pH was 7. After 3 hours the crystals were filtered off and washed with water (3+5 ml). The crystals were dried at 40° C. under reduced pressure over night to give 4.4 g partly crystalline neutral **S-omeprazole** form B.

CLM What is claimed is:

1. **S-Omeprazole** in a neutral form, wherein it is in a partly crystalline state.

2. **S-Omeprazole** according to claim 1, wherein it is in a substantially crystalline state.

3. **S-omeprazole** according to claim 1 or 2, wherein it is in form A.

4. **S-omeprazole** according to claim 1 or 2, wherein it is in form B.

5. A process for preparing **S-omeprazole** according to claim 1 or 3 which comprises crystallizing the **S-omeprazole** from a solution comprising neutral **S-omeprazole** in one or more organic solvents and optionally water.

6. The process according to claim 5, wherein the solution of neutral **S-omeprazole** is formed by dissolving **S-omeprazole** in the organic solvent.

8. The process according to claim 5, wherein the solution of neutral **S-omeprazole** is formed from a chemical reaction solution comprising **S-omeprazole** in an organic solvent.

9. The process according to claim 5, wherein the solution of neutral **S-omeprazole** is formed from an extraction phase comprising **S-omeprazole** in an organic solvent.

12. A process for preparing **S-omeprazole** according to claim 1 or 3 which comprises precipitating the **S-omeprazole** from a solution comprising an alkaline salt of **S-omeprazole** in water and, optionally one or more organic solvents, by adding an acid to the solution.

13. The process according to claim 12, wherein the alkaline salt of **S-omeprazole** is dissolved in a mixture of water and an organic solvent.

15. A pharmaceutical composition comprising **S-omeprazole** according to any one of claims 1, 3, 4 or 5 as active ingredient in association with a pharmaceutically acceptable carrier.

16. A method of treating a gastric-acid related condition which comprises administering to a patient in need of such treatment a therapeutically effective amount of **S-omeprazole** according to any one of claims 1, 2, 3 or 4.

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